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22nd Meeting
National Bioethics Advisory Commission
July 14–15, 1998
Portland Marriott
Oregon Ballroom, Salon F Oregon Ballroom, Salon F
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Portland, Oregon Portland, Oregon

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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 decision-making 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 carefully about 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 work.

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 us, being those who are considering this issue meant 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 seeing well, 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 consent and 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 current 

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 that well, 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 samples\(\chi\) those 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 under\(\chi\)

**M R. C A P R O N:** 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.

**M S. C H A R O:** 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 research\(\chi\) and I have a feeling now Steve Holtzman and Carol Greider are going to flip when they read the transcript\(\chi\) in 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.

**M R. C A P R O N:** 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 granted\(\chi\) I'm always glad when I get expedited review, because it's easier\(\chi\) but 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?

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

**M.S. 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?

**D.R. SHAPIRO**: Alex?

**M.R. 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
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.


M S. C A R O : 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.

D R. S H A P I R O : 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.

D R. C O X : 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.

M S. C A R O : You been talking to my mother again?

[Laughter.]

D R. C O X : 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.

M R. C A P R O N : 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...

D R. C O X : 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.

D R. S H A P I R O : 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: Well 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.

D R. S H A P I R O : David?

D R. C O X : 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.

D R. S H A P I R O : 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: I think 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

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.

D R. S H A P I R O: 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.

M S. C H A R O: 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.

D R. C O X: 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 those

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.

M R. C A P R O N: 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.

D R. S H A P I R O: Alta?

M S. C H A R O: 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.

D R. S H A P I R O: 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?

M S. C H A R O: 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 Melody Lynn knows the date, if she's in the audience she can confirm it of 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 which

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

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 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 their 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 Diane 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 then X and I think so 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 been currently in use, if I understand what people are saying. And then the question is just how do you deal with the what'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 point Bernie 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 although 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 received and some of you are much more knowledgeable than others or 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 the 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 you 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 the well, 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 concerns this 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 it, I'll get of 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.

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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 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. MIKE: 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 with back 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 appropriate to 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 for 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 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. MIIKE: 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 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 you 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 a study, 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, benign and 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. We and 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 was as 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 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 presumably there 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 were and you maybe were afraid, and nobody was going to listen to you. That's all. I just you know just have a visual image of how that would effect the subject.

MR. CAPRON: Well, I just this 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 really are two issues, which we've collapsed a little bit in this
discussion. One is the issue of whether you need to do there 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't if someone says when 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 giving raising 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 of

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 the 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 recommendation are you saying at 162, where we give the recommendation? Because I thought that the way those recommendations usually

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

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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? O ne comment. O n 162, are we going to have trouble when we qualify the word "dissent" by a parent? That seems pretty big standard.

D R. M I I K E: But that's the Commission talked about overt. W e're talking basically about dissent. But if we see an apparent dissent, that's it should be a lot more in the opposite direction.

D R. C H I L D R E S S: Any form of resistance. F or example, going to an M R I. S o, it is it's much broader. W e capture a lot more people that way.

D R. M I I K E: W ell, I'm just a little worried of how full and apparent as the qualifier of what he said.

D R. C H I L D R E S S: And we've had some discussion about it. J onathan, do you want to say anything about this?

D R. M O R E N O: 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. I f one were to say, "no dissent," then clearly one could construe that in a much stricter fashion. D issent means for us such and such. I t 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.

D R. M I I K E: Instead of apparent, could we say expression of dissent? A n apparent, one gets to be very subject, in terms of what one can an expression can be an expression, verbal, nonverbal, etc. Anyway just consider that. T o me apparent is so vague, that it's just wide open.

M S. L E V I N S O N: But maybe one would want to put in "expression," and then parentheses, verbal or nonverbal. I t makes it more specific.

D R. C H I L D R E S S: H arold has mentioned that indication is a possibility, no indication of dissent, which would be another way to go.

M S. C H A R O: I t 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 other transient thing. A nd 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 think you 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?

M.S. 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.

D.R. 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
hereI62, 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.

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

M.R. 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, as 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. 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. 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. 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. 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. 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. 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. 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.
of IRBs, in terms of X 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 why we choose the bottom lines as we do, rather than other bottom lines. 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 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 has been a terrible problem.

DR. LO: But then what happens? I mean 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 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 not 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.

Why 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 into

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 be don't know a 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 re-interviews 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 write that 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 offering correct 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 recommend. I guess I'm not sure if we would exclude that. I think it would. I 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 that we would exclude that. I 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 that we would exclude that. I think it allows that. Well, at the very least, we could articulate exactly what it is we'd want to say here. 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. 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. This.

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 is that 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. MIKE: Well, the way that it says, subjects with mental disorder, any if 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. MIKE: 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 to if 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 first X 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 of if 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
custom 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 bioethical 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 am 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 it the 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 to the 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 and

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.

M.S. 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 and 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...excuse me. One more private citizen, whose 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 improving technology, and limited controls. And, finally, to when 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 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 increased the 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 would the 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.

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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 also and we’ll turn to Bette in a moment but 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 some of them in the two reports that are will 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 centralization 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.]
DR. SHAPIRO: I have just been informed Dr. Childress has been called to the phone, but he'll be back here in a few moments. But we are going to, again, move some of our agenda forward. Dr. Mary Claire King is here, and she is going to speak to us on genetic research, individuals, families, and communities. And, really, we couldn't have anyone better do that, and a more experienced understanding in this area, a very distinguished professor of medicine and genetics at the University of Washington, and well known from so many things, I won't take time to enumerate them all, if you will forgive me. But it's a real pleasure to have you. We are very honored that you took the time to come down here to share some of your thoughts with us. Thank you very much for being here, and thank you also for all of the work you've done over the years that's so relevant to so many people. But welcome, it's very nice to have you.

DR. KING: Thanks very much, Harold. I have to tell you all something that only Harold and I know, and that's the real reason he's ever heard of me at all is that my brother graduated from Princeton and has been a royal alum for many years. And Paul was in the last of the classes which were male only. And since he's my younger brother.

DR. SHAPIRO: Don't hold that against him.

DR. KING: I didn't go to Princeton. Had you reformed a bit earlier, I would be an alum myself.

DR. SHAPIRO: All right. This meeting is full of tragedies.

DR. KING: Perhaps, mine as well. It's both a privilege and daunting to speak to the Committee, because I'm very much like one of those children who moves to town when the semester is well underway. You all have addressed every issue I could probably bring up. And in many ways there is no wisdom I, as one individual, can add to what you haven't already discussed. What I thought I would do is tell you from our experiences that go back to 1974, three different studies that we've been involved in all happen to be breast cancer studies. Because, of course, that's a major interest of mine. And in each of these studies, which are quite different from each other, just name some of the issues that have arisen and how we dealt with them, and where we see problems, and where we see opportunities, and so on. But let me start by stating my premise of where we've come from philosophically in just a few sentences. First, that to some degree scientific evidence to the contrary, notwithstanding, the questions of genetics, genotype, and genetic identification are, in my view, different from those of any other medical problem. The
parallels with HIV are real, but the differences are real, as well. The parallels with any other concern for privacy are real. The differences are real as well. There are I think two fundamental reasons for it, which are human and not scientific. The first is that everything that is genetic has implications for our children, and nothing is any more important to any of us than that. And, second, that an enormous amount of murder has been committed in the name of genetics, and we would be extremely naive to believe that that's finished. Our human rights work in the former Yugoslavia now is like dramatic evidence that even though we are working with three populations of people, which, when you overlay their genotype are indistinguishable, nevertheless are engaged in patricide against each other of scientific evidence, to the contrary, notwithstanding. So, I take enormously seriously the work that you've set for yourselves. I consider it a blessing that you are doing it. It's not fun. It's not easy, and thank you very much for spending the hundreds and hundreds of hours you're spending on the problem. So let me tell you a little bit of our experience, and then just reflect with you on what it means and what use it might be to you. First, our project with families with multiple cases of breast cancer, a project that led over a couple of decades to identification of two genes which are responsible for inherited predisposition to breast cancer. In this project, we were working with very large families in which breast cancer and ovarian cancer are extremely common. The work began in the era before even DNA analysis could be done. And, of course, proceeded into the era of DNA analysis and was dramatically shot forward by the development of PCR. From the time of the invention of PCR, the availability of sources of DNA from persons who had died of the conditions of concern to us, that is, from people who were in the original generations of these families and had died of breast cancer decades before became critically important. BRCA-1 could not have been mapped, let alone found, without the use of specimens from pathologic materials from individuals who had died of this disease long before our project was ever undertaken. It was also, of course, essential that we know, specifically, who each sample belonged to. It's not a question of an optimizing sample, such as a matter of it being terribly important that we have my grandmother's biopsy specimen, in order to obtain DNA, both from the normal cells and from the tumor cells, and to work with both. The way that we addressed this question was to ask the next of kin of the persons who had died, if we could work with the pathology specimens from their deceased relatives. Sometimes that was a widower; very frequently, it was a child. This offered us no difficulties. We carried out that work. We kept the names attached to the specimens as we were working through them. We talked to people about their relatives directly.
very open communication. Of course, when we published pedigrees we were and are very
careful to publish pedigrees in such a way that people who are still unaffected and young
do not have their genotypes identified. They are simply excluded from pedigrees. But
there is no question that we worked, and continue to work, with specimens from persons
who, themselves, are in no position to be able to give us informed consent, because they
have died and are never heard about. And those specimens are critical to gene-finding
activities. So this is really an example, this first class of studies, of studies that involve
retrospective materials, stored specimens with known people, where we do get permission
from next of kin. The second kind of studies is exemplified best by our New York Breast
Cancer Project, which is a project that Joan Marks and I are undertaking with now 12
institutions in the Greater New York area. This is a study of breast cancer among women
of Jewish ancestry, who are breast cancer patients. It has really two goals. The first is to
understand what the actual risks associated with BRCA-1 and BRCA-2 are; and the
second is to understand if those risks are in any way modified by other genes, or by
environmental exposures, or beneficent life events. The design of the study, to tell you
just real briefly, so you'll see where we're coming from, is that every woman who is
diagnosed with primary breast cancer in any of these institutions from 1994 to the
present, regardless of her age at diagnosis, and regardless of her family history, is asked to
participate if she self-identifies as Jewish. It is entirely self-identification. If she says, "Yes,
I'm Jewish, and, yes, I had invasive breast cancer." Then she's asked to participate in the
study. This is done through a stepwise genetic counseling process, which incorporates
genetic counselors, who are the genetic counselors of their institution. So, it is a formal
clinical genetic counseling process. She gives a blood sample. We genotype that sample
first for three agent BRCA-1 and 2 mutations that are found in Jewish families. And if I
won't get into the question of what about people who are negative, but from high-risk
families. That's another project entirely. But if, for this project, if this person this patient
has one of these three mutations, she then becomes the index case for a family, her
family, and we work with her to trace the genealogy of the mutation in the family,
regardless of the cancer status of the persons with that mutation, in order to obtain
rigorous properly ascertained estimates by age of risk of breast cancer and ovarian cancer
associated with mutations, and the interaction with potential environmental factors that
I've told you about. Any person in this project who wishes genetic information back for
themselves receives it and receives it with pretest counseling and posttest counseling, and
no one is involved in the project until they have agreed and had pretest counseling. It is
about 95 percent counseling, and about a 5 percent genetic analysis, so it's going along.
As you might imagine, it's elicited a lot of interest in the New York medical world, and in the New York Jewish world. And, oh, sometime last year, some staff members of Hadassah became particularly concerned about this project, and I think some others. The exact history of what their origins of their concern elude me a little. But a consequence of their concern is that a fascinating meeting was held, sponsored by Jewish organizations in New York with senior officials of our NIH. Rick Cosner was there. Francis Collins was there. I suspect others as well. I did not attend. I was not invited, as it happened. But many of our clinical colleagues did attend. And the American Jewish Congress in the person of Lois Waldman, who is a lawyer, who works with American Jewish Congress, prepared a statement about genetic diseases in the Jewish community, which I've just received from Lois, and have consequently distributed to you. A number of us were asked if we were interested in signing the statement, and I very enthusiastically did so. So, my name is checked down here. To make a complex story short, I believe that the denouement of this experience was the following: That stigmatization, the possibility of stigmatization was directly confronted in discussion and was acknowledged as a real and legitimate concern. But that there was passion for not stopping biomedical research as a consequence of that concern. And there was, in particular, great concern that informed consent be individual, that every person have the right to either participate or not participate in a study. And if they chose to participate, to either participate anonymously, or not anonymously, and that the individual's right to make that decision for herself or himself be retained. I'll point out just a couple of the relevant paragraphs to you. But, like I said, I refer you to Lois's statement in general. Her comment at the bottom of page six, "Throughout American history, Jews have insisted that they be dealt with as individuals, not as some corporate body as in medieval Europe," and so on. And then toward the end of her remarks, "Genetic researchers and members of the Jewish community should maintain an ongoing dialogue, so they each may be apprised of the others concerns about genetic research involving Jews. The Jewish community should support passage of legislation to correct loopholes in existing law banning genetic discrimination in health insurance, and also support bills to prohibit genetic discrimination in employment, and to protect the privacy of all medical records," and so on. Development of this project in New York passed through IRBs at all 12 of the institutions, with whom we work, and, of course, at the University of Washington. And the concerns raised there are very much the ones that your Committee has been dealing with; that is, the ability of the individual to make informed consent. Since this is a prospective study, many of the issues that we're dealing with today don't arise. However,
the same question that I just brought up, namely, the working with specimens from, for example, mothers of persons who have died, may come up in the future. So, it's not necessarily buffered from that entirely. Because of the unique issue of working with one of America's remarkable populations with a still coherent genetic ancestry, I have realized for myself early on that I needed to know a lot more about Jewish history in America. I am just parenthetically one of these persons who learned only as an adult, that she is in fact partly Jewish. Madeline Albright is not alone. It turns out my mother was born a Cohen, and I learned that after my daughter was born. American history is full of these stories as well. What we decided to do, in order to educate ourselves was to establish before we began the project an advisory committee, not an IRB, but an advisory committee to educate us about what we and by we I mean Joan Marks, and the oncologists, and the clinical geneticists, and the counselors, and I thought of as the critical kinds of issues that were likely to arise from our participants. Stated socially, what does it mean to be a Jew in America? What does it mean to be a child of persons who were survivors of the Holocaust? What does it mean to be both an Israeli citizen and an American citizen? What about our collaboration with our Israeli colleagues? I haven't discussed that, but we have an exactly parallel study going on in Israel by a collaborative group there. And this committee meets about once a year. And, importantly, has undertaken education of genetic counselors in New York about those issues. So, it's been for me an enormously enriching experience to have that committee involved. They have not been a hoop through which we needed to jump. They haven't had any veto power over the study at all. They never asked for that, and that was not the purpose. But they have been enormously helpful in suggesting how to do it right. There has been mutual respect and we're learning a great deal. The third project I want to discuss is, yet, again, different. This is a project which is just now getting under way. It's our collaboration with the NSABP, and their tamoxifen prevention trial. As probably most of you know, the tamoxifen prevention study of the NSABP has just released its first results. The nature of this project was that women who were at high risk of breast cancer by dint of family history, or age, or personal threatening history, but not actually having ever been diagnosed with breast cancer were asked to volunteer for the project. And if they volunteered for the project anywhere between five and eight years ago, were randomized to either tamoxifen or placebo, were asked to remain on the regimen to which they were randomized for five years. And at the beginning of this study no one had breast cancer. Thirteen-thousand women volunteered for it, were randomized 50/50 into two groups, and the study proceeding forward triple-blind, with neither the women, nor the
physicians, nor the investigators knowing who was in which category until one committee, which consisted of only three statisticians, in evaluating the results reached a stopping rule, which had been previously defined on the basis of statistical grounds. So when the stopping rule was reached, that is, the stopping rule was either the tamoxifen would have a benefit that was significant at a preordained statistical level, or would have a detriment that was preordained at a statistical level. When that stopping rule was reached, the results were revealed. That happened, it happened earlier than they had anticipated. The results of the trial are that tamoxifen that the women who were randomized to tamoxifen have 40 percent fewer breast cancers than the women randomized to placebo. Concomitant with that, the women randomized to tamoxifen have higher risks of endometrial cancer, so this is not one of these entirely beneficent situations, and each woman needs to decide for herself. And that’s a whole set of issues in itself. My interest in this for the last eight years has been whether women who would turn out to have inherited alleles predisposing them to breast cancer, would be particularly benefitted, or particularly not benefitted by taking tamoxifen. One could make the argument either way, depending on how one interprets biological roles with BRCA-1 and 2, which is hardly a settled matter either. So what the study that my lab designed with the NSABP and the NCI is to well, I need to also tell you parenthetically that each woman at the time that she entered this study gave a blood sample and signed a consent saying that this sample could be used for investigation of biological markers. There was no specification to BRCA-1 and 2, because they weren’t known yet. They weren’t named by name. So, the study we designed from the purely design point of view, was to take the blood samples from all of the women among the 13,000 who had developed breast cancer. And about three women from the cohort, who had not developed breast cancer for each woman who had, so about a thousand samples in all. To genotype in my lab, all thousand of the DNA extracted from each of those blood samples all the way through BRCA-1 and all the way though BRCA-2, so as to determine who had mutations in those genes, and then to answer to questions. What is the absolute benefit or detriment associated with using tamoxifen if you are a mutation carrier? And what’s the relative benefit or detriment? There, clearly, is not going to be a way to say this with any level of significance, but we will at least get some point estimates. The question, of course, arises, how does one do this? To what degree does one anonymize? I used to think anonymity was like pregnancy, but I now realize it is not like pregnancy, that there are degrees of anonymity. Right. So, we turned to the Participant Advisory Board of the tamoxifen or of the NSABP, and, in particular, of the tamoxifen trial, who are women who are on the
trial, and discussed it with them. To take a couple of extremes: at one extreme, we would have attempted to go back to every one of 13,000 women and asked if we might put their name into a hopper to be randomized to being in the trial or not, and not have put their name into that hopper, unless we could obtain that consent. That was not feasible. As in any other large randomized trial, large numbers of people drop out. It was possible to follow people's ultimate cancer status through publicly available records. But something like 15 percent of people from each arm had dropped out, just as people do, and we would have had a highly incomplete follow-up had we tried to go back to every woman and get explicit permission to use her sample, and we would have had a serious bias to the trial. So, I said I would rather not do the trial after that. Also to take the opposite extreme, we would have tried to contact every woman and give back to her, her individual results. I also oppose that, as did the Participant Advisory Board, because the samples, although they were collected by sincere, extremely well-meaning investigators, were collected at hundreds of different hospitals. They weren't collected using clear guidelines. There is always the possibility of sample mix up. And while that's a detriment to a statistical analysis, it's devastating to an individual. So, if someone needs an individual result, they really have to do it properly with prospective collection of sample. So, we were really left with some intermediate possibilities. One was to...
that they and we perceive that they're going to need. So, this is all material that's been obtained up to this moment. For example, do they have cancer or not? What year were they born, and so on? And that's put into a separate file with the consecutive number. We do the genotyping. We give the genotypic information back to the statisticians at NSABP, and together we do the analysis and we get an answer. The critical question then is, is the link between the identifier in NASABP, it's original identifier which, of course, could then be traced back to the woman herself and the consecutive number kept or destroyed. The way that this study now stands, and the way it's been passed by all of the IRBs, that link is destroyed. The reason we decided on that is that this committee hasn't finished its deliberations yet, and we don't know what your wisdom will be and we want to be conservative. The downside of this is that we will never be able to do...

DR. SHAPIRO: Say that one more time.

DR. KING: I said we don't know what your deliberations will yield. It's perfectly possible that your deliberations will lead to a recommendation that studies of this type be completely anonymized with no possibility of anyone ever getting back to the individual, which we will not now be able to do. And we don't want to put ourselves in conflict with this Committee at any time in the future. The downside is we will not ever be able to do the survival studies, and I am very concerned about that. The Participant Advisory Board is, if anything, more concerned than I, but it is the price we've paid. So those are three of our experiences, and those are where we stand. And I have no special wisdom that's what's up. I'd be happy to talk with you.

DR. SHAPIRO: Thank you very much for describing these studies, and this is not my area of expertise. But I really, and, nevertheless, must say I'm very impressed with the care that you've taken in proceeding in studying diseases in this particular community, and it sounds very impressive! I'm sure to my colleagues as well. I have a bunch of questions, but let me see if other members of the Commission want to speak. Yes, Diane, then Bernie.

DR. SCOTT-JONES: Thank you very much. And I have a lot of questions, but I'll limit myself because I'm sure everyone else has questions for you as well. I was very impressed that it seemed that your learning about the Jewish community in your work was something you saw not as a burden, but as an interest in the population that you study. And I suppose that the ideal, and how we promote that through the variety of mechanisms that become available to us for promoting scientific standards and ethical standards probably promote just what we did.
DR. KING: I think it's terribly important that the role of the citizen advisor, as educator, and the role of the IRB, as regulator, be separated. We need citizens on both, but I think they are different roles.

DR. SCOTT-JONES: Could you say more?

DR. KING: On our committee that Joan and I put together anyone who knows Joan Marks, knows that for Joan Marks to put together a committee like this in New York, where there are people pounding on her door to be on it before it was over includes a psychiatrist, a historian of Holocaust studies, a journalist, no one medical. The other people are women who are philanthropists, and I don't know their original professional training. But everybody in the committee is Jewish, except me, then it turns out I am, too. I didn't know when we started all of this. So, anyway, what that committee does is educate us and help Joan, and to a lesser extent me, establish lectures, and seminars, and courses, which are required for the counselors who are involved in the project. That's teaching. That's not the same thing as our going to them as an IRB and saying we need your approval for this. It's a mutual teaching process. And I think it allows us, as scientists, to let our hair down, and to express our insecurities over these issues. I mean to take one very dramatic example. I said we encounter almost no one who has inherited mutations who is elderly and has not yet had breast cancer, but there are a few. And one is a woman who is a Holocaust survivor. She since died, but she was alive last year. She's in her eighties. I said how is anybody going to talk to this woman about her experiences as a young woman? I mean this is completely beyond the experience of anyone, and we worked out a way to have this person interviewed with the help of a person for whom this was not beyond their experience. And I was able to admit completely freely my need for help in that area. That's very different than a regulatory process. So, teaching and regulation are both essential, but should be independent I think.

DR. LO: I, first, just want to thank you for a wonderful presentation and a lot of food for thought. Two questions for you about the tamoxifen study. The first has to do with deciding whether you can use someone's sample. Others have suggested that in a study like that where you really have a well-defined population and a participant advisory
board that there be some sort of surrogates for individual consent since you have to have 95 percent of the people who you can contact that would agree their samples to be used. That gives you perhaps some ethical warrant to do more than the opt-out. So my first question is about your thoughts on the other options you could have employed. My second question, which I think really is directly in line with some of the issues we've debated, is how you handle the double coding at the NCI and then the code that's given to you with your thousand samples. At one point in our deliberations, we had talked about the status of the sample as the researcher has it which may be different from the status of the sample in the original repository. So as I understand it, the NCI can link everything...No, but it passes its use in a way that you can't link back to the original but they can feed you certain information. And what your case really illustrates is several things, but one is certainly the cost that you pay when you give up not being able to retrace that linkage. And let me elaborate what I think is the situation. I mean in breast cancer disease, you know it's a 20-year disease, and so whatever trends that were strong enough to prompt the stopping of tamoxofin are of marrying up the totally predictive of long-term trends. And so this is a disease where if there ever was a disease where you'd want to be able to walk back and get feedback at 10 years, 20 years, on the incidence of the cancer, this is one of those. So that's one thing, just that we keep in mind the cost of policies that are intended to enhance individual autonomy and things like that. But the second point is that we have also considered what may be in fact computer science fiction: but encryption schemes, where you continue to be blinded to the ultimate identity of the patients but you're able to get updates on the breast cancer status of the sample through the central registry as they get it from whatever cancer registry direct. So it seems to me it would be important to try and develop both the technology to do that what we've called sort of one-way communication both to really look seriously at the technical ways of doing that and still protect confidentiality, but also to carve out the ethics of that because it seems to me your case is an example where my initial reaction is, let's try a way to protect those people who really don't want to know of, don't want to be bothered by recontacting, but somehow to also answer the very pressing scientific questions that you played out, which ultimately, I think, are really going to provide tremendous clinical benefit to people at risk for the devastating condition. So I think it is really going to help us to try and puzzle through this third case with you because it really touches on issues that we have struggled with. I guess my final point is that I guess it bothers me that because we haven't said whatever it is we're going to say, people are rather trusting their best judgment, it seems to me that everything we've heard and everything I know about your work is that I would trust you as an investigator with your colleagues.
and your advisory boards to do the right thing in ethically perilous territory. I think there's a cost to the perception that until we've made a decision, investigators take the most "conservative approach," but it's conservative from a certain point of view, it's very wasteful from another point of view. And I think that's something we have to...I mean colleagues of mine have expressed their concern at our not making some sort of statement, which then may or may not get picked up as policy, but I think your case really drives it home that our not acting in a timely way is having a real impact that's not going to be reversible on studies that I think anyone would say are really important, significant vital signs that need to be touched.

D.R. KING: That's exactly right. The...it's not scientifically or medically justifiable to do what we are doing because we will not be able to answer the question if a woman develops breast cancer and had an inherited predisposition and was on tomoxofin, is she best advised to have another round of tomoxofin, to stay off it, is her chance of recurrence less because she's already been on it. We won't get any of the that information about people with inherited predisposition because we won't be able to follow them up. The way our coding scheme works is that the way it's set up to work right now is that the NSAPB statisticians who are the people who actually do the analysis who, incidentally, are superb, will make the file of the basic clinical outcomes as they now stand and the basic demographics that they need. They'll put that file in place. Then that file will have numbers attached to it, which will be the same numbers that will be given to the clinical laboratory who is doing the DNA extraction, and then the link will be broken. I will get the DNA samples with only numbers one to a thousand on them, and by that time that's all that will be on the file that the statisticians will have, so none of us will have the linkers. The material from the clinical laboratory will go back to the repository with the original numbers on it, but those numbers will no longer have been physically on the same tubes with the one to one thousand on them so nobody, short of reverse genetics and sequencing the entire gene of the sample, nobody would ever be able to go back. There are ways—and the statisticians developed one when we were more optimistic about being able to do follow-up for clinical outcome of doing encryption so that I, as the geneticist, don't ever learn who these people are. I don't need to know that. However, there is no way you can have clinical outcome and not have some human being know what all the information is on that person, someone has to be able to know. Now, bearing in mind that these are people who are caring for these patients, it is an extreme position to take to say they don't have the right to have any of this information, but that's what we've said. To go back to the surrogates versus the opting-out strategy, again, we
took the most constrained route. It has added, oh probably, eight months to getting the study started, and it's added a great deal of cost. In this case, the NCI was prepared to sponsor that cost so we were all right. It has had, I think, real costs in public health costs because when we decided on the opt-out strategy rather than the surrogate strategy, none of us thought that the results of the trial were going to be coming online so quickly. And consequently, we thought we had a little bit more time to play with. The reality is I still don't have those samples in hand. It's going to take me a year to 18 months to do all this genotyping and I haven't even been able to start yet, and I've been talking like this since 1990. So this is not a good example of getting something done in an efficient way, and yet, everybody involved knows what they're doing. So there's got to be a better way, right?

M.S. CHARO: I always hoped this Commission would have an impact, this is not the one I'd hoped it would have. Mary Claire, if I understood the protocol correctly with regard to situation number three, the tamoxifen study, the only thing that you would have had to do differently in order to be able to retain those code links and get all the follow-up that you want, and still be in compliance with the federal regulations, the only thing you would have had to do is to have sought consent as opposed to simply having an opt-out provision. You were already mailing to people at known addresses, and you chose to mail out something saying if you don't want to be in here, mail this back. If all you had done was to mail something out that said, Would you be willing to participate, you could in fact have kept all those links under the federal regs, no problem. You would have met every requirement. And since up until now, as of now, the discussion on this Commission has been really about how to enhance enforcement, appropriate enforcement of those existing regs, it seems particularly tragic you would have destroyed those links. I'm asking how much more expense, how much more delay, how much more sample size reduction do you think you would have had if you had taken that last step in order to uncomplicate your lives and allow yourself to get the updated info?

DR. KING: It's a scientific problem, and naturally we discussed it. The difficulty is that the people that you lose by an opt-in strategy are not a random sample of the group as a whole. For example, you lose all the women who died of breast cancer. And you also lose all the women were lost to follow-up for the trial. And that's a lot of people and they are not random. If they were random, it wouldn't change your point estimate, but we did simulations on how much nonrandomness/randomness in order for us to follow up,
rather, for death or other reasons we could sustain and still have a meaningful response, and decided it was potentially devastating to the results, that we couldn't maintain the statistical rigor.

**M.S. Charo:** Just a clarification on this, if I may? For those who died, their samples could be used without any kind of consent because they're not considered to be subjects under the regs and you're allowed to use their stuff with impunity. The question being, could you know who those people were so you'd be able to pull the samples out of those people who are now dead and say, fine, these are okay, and add them to the samples of the people who'd opted in. So, in fact, it would have been...it might have been possible if you can identify them to have gotten at least that subset of nonconsenters back into your sample, leaving only those who actively, who failed to consent and are still living. Either lost to follow-up or genuinely failing now.

**Dr. King:** Right.

**M.S. Charo:** Earlier today, Diane was talking about some of the challenges of statistical validity that always exist in study design and I'm now getting interested in understanding exactly how significant this problem is as compared to the general problem of validity that Diane talked about because the current regs, if the current regs have this high a price, we should be very much aware of it.

**Dr. King:** This, of course, is the world I come from, and it doesn't take very much ascertainment by us to throw point estimates off drastically. I think had it been only a matter of the decedents we could have dealt with it. The greater difficulty is that when everyone asks 13,000 people to send back a card saying they're opting in, your response is very, very low. And the cost of going back and back and back and back and getting that up to 80 percent, let alone higher than that, is extremely high. Then you have to prove to your own satisfaction that the people who haven't responded are not biased in one way or another. It's...it was the statisticians that basically drew the line. We did a little pilot and the response in sending back the card to the pilot was something like 30 percent, 70 percent nonresponse.

**M.S. Charo:** And this was with highly motivated, educated, newslettered people.

**Dr. King:** Oh, terrific people, newslettered people. Basically they're probably newslettered to death, but what can I say? And it wasn't that they weren't interested. I mean you follow up with this little pilot and you say why didn't you do this, and they say, oh, but you already have my sample, of course you can use it, oh geez, did I not send it...
It's a big study. And it's a sort of a specimen of these large trials that one will need to confront.

DR. SHAPIRO: Other questions? Let me go back to something you said right at the very beginning in dealing with genetic information, and your own view as to why it's different from other kinds of information. At least as I recall, one thing you mentioned was that it had implications for one's children and so on downstream. And the other I wasn't quite sure that I understood what you said. It sounded to me like you were saying this kind of information's been misused in a serious way, very often in a historical sense, or be used for...I didn't quite understand. I mean I understand what's going on in the former Yugoslavia, but I didn't quite understand how that related to genetic information.

DR. KING: I think the point I was trying to make is not that legitimate genetics has been used that way, but that all of our concerns, just as citizens, not as scientists, about the way that a stigmatization, racist arguments, and eugenic arguments have been used against people are real. No question about it. The fact that it has, the fact that one can use population genetics correctly to debunk those arguments is important. But it is not sufficient. It is not sufficient for me as a geneticist to be able to say look, there's nothing new here, this is all the same as it was before. There are too many historic counter-examples. So what I'm saying is that the problem is a historical one and not a problem with genetics itself. Does that help?

DR. SHAPIRO: Okay, no it's very helpful. Let me ask you about what I think was the second experiment, or second...well, it had to do in any case with the need when someone is deceased. You went to their next of kin. And I was trying to think here how you figured out who that was. They might have had two children, they might have ten children, they might have I don't know what. How did you figure...and what if they disagreed? Let's say there were just two children and they disagreed. How do you deal with issues like that?

DR. KING: Right. Typically the way families come to us is by self-referral or referral of a physician of one case. And we quickly become bonded with the family, with lots of people in the family. So very frequently next of kin for example, if a woman's mother has died and a father's long since deceased also we ask that woman for permission. We have not had the worst possible scenario in that, a situation in which there were, let's say, two daughters, and one said don't you dare look at my mother's
sample and the other one said I insist that you do. That hasn't happened. We have had a number of times a situation in which one daughter has said I want the study to proceed, I want our mother's sample to be used, and the other daughter has said I don't want to be part of this. And then, as you can see, we proceed. And the issue of intrafamily confidentiality is what becomes enormously important: the daughter that doesn't want to be part isn't part. I think what we would do...the scenario you bring up is analogous, I believe, to a scenario that has happened, a number of times, in which we know a woman's genotype, we know that she has a predisposing allele, and she doesn't want us to tell anyone in her family. Or in particular, she doesn't want us to tell a younger sister who is at risk, 50 percent risk, of inheriting the allele. And we are bound not to tell that younger sister. We work on it over months. That's why genetic counselors are trained the way they're trained. And we simply discuss the issue with the person and hope that in time the person will come around. I think, and so farALKnock on woodX each time that's happened they eventually have. There are all kinds of personal things that come into it; eventually each time it's worked. I think if we did confront the scenario you present we would do the same thing. We probably wouldn't use that sample until we had gotten past the unhappiness of the other sister. But we'd just keep talking to them. We're talking about real people here, and we have real relationships with them, and the relationship doesn't stop when we know their genotype.

DR. SHAPIRO: If you wereX and I apologize if I don't ask the next question in a coherent way, I'm not sure I have a coherent question, but there may be something hereX if you were trying to design a study which required genetic material from lots of members of the family, some of whom were deceased, and then going on a few more degrees in one way or another, and the question is for the deceased relatives, the deceased kin this case. There's some misunderstanding...there's some kind of ambiguity about current regulations, whether they are human subjects or not. On one hand they're not; on the other hand, they have information which impacts other people who are living and one could argue that they are. Our understanding of current practice is deceased is deceased, and this other issue is they're just not treated as human subjects for the purpose of the regulations. But the kinds of studies that you're concerned with and deal with, would it be a huge and super\textcolor{red}{X} not be huge\textcolor{red}{X} would it be a significant barrier if you were told that if you want to use the material from deceased kin that you have to get permission, as you've mentioned next of kin, whoever the first living relative is with the oldest living relative, would that be a significant barrier, an irrelevant barrier, a big problem, small problem, if we began treating these deceased individuals in this sense as
kind of human subjects? When you consent of one form or another from their living relatives.

D.R. KING: Are you referring to a situation in which I, as the investigator, need to retain the identification of the person?

D.R. SHAPIRO: Yes, right.

D.R. KING: Right, because for the anonymous case it doesn't matter.

D.R. SHAPIRO: That doesn't matter.

D.R. KING: Right. I think any, whenever anyone is working with real families, any regulation that sets any one policy in stone is probably asking for trouble. I think that...I have no problem at all in asking for a next-of-kin agreement. We've always done it, and I can't imagine that we wouldn't always continue to do it. It's simply a matter of showing respect. What I would find very burdensome and would probably mean it would probably be a deal-breaker for me, I probably wouldn't do this work any longer if I really had to go to everyone in the family because that forces people into dynamics with each other which they may choose to avoid. And it destroys the privacy of the individual. And so I think this becomes one of those situations in which it's necessary that individual investigators and individual IRBs and individual genetic counselors who are after all trained in this kind of thing see cases one-by-one, and when it makes sense to work with this daughter rather than this daughter that they be allowed to exercise that judgment. But that families be respected and that there be "a" next-of-kin permission granted. That in itself I don't find and anathema at all.

D.R. COX: So, Mary Claire, I, too, would like to thank you very much for coming because you give a perspective of a person in the trenches who's thoughtful about this, that I think that oftentimes we don't get before the Commission. Having said that, though, I'd like to come back to this issue with respect to the bias in the sample from a scientific point of view because I'm having trouble with this. I'm not an epidemiologist and so I really am seeking clarification on this. Certainly I can envision that if you had only 30 percent of the sample it could be biased, but it might not be. And I don't have any idea for figuring out whether it is or not. On the other hand, doing an opt-out, even if only ten percent of the people that opt out, how does one know that those don't bias the sample? So I'm having trouble with the logic here.

D.R. KING: Right. There's a huge statistical field devoted to this problem, right?
The way that one can determine whether one's opters-out are biased is that a person this all happens before there's any randomization at all into my study one's opters-out send back their cards and the statisticians can say, "Right, the people who are opting out are people who are over age 70." Right? And if it's something that simple, one says right, this project, therefore, is generalizable to people under age 70. If the people opting out are people with a family history, that poses something different in terms of genetic analysis. The relationship between multiple, independent variables influencing a trait and the degree of disproportionate opting out that one can sustain, and the consequences of that for point estimates are, as I said, a matter of statistical analysis for which there are protocols that one follows.

DR. COX: But that approach could really screw you, too, right? Because the people that choose to opt out could be very nonrandom and it would make it very difficult to use the study.

DR. KING: Right.

DR. COX: So I see that you could get screwed in either direction.

DR. KING: You could, in principle. However, in or experience with lots of different opting-out and opting-in pilot studies and real studies, asking people to opt in when the sample is very, very large is enormously expensive and fundamentally unwieldy. Opting out simply works better because there are far fewer people...people, if they don't want to be in a project, are much more willing to send in a card saying I don't want to be in a project than are people who are willing to opt in. I mean, I myself, as a subject, without realizing it when it was at Kaiser, of one of these opt-in studies, I forgot to send the card back. It's just something you have to remember to do.

DR. COX: So I understand that point. It's the point that you just made was an unwieldy one, but not a scientific one.

DR. KING: But it becomes scientific, David, because if only 30 percent of the people send a card back saying yes, I'll be part of the project, it would be remarkable. It would be testable and remarkable if those 30 percent were a random sample of the overall group. And chances are they won't be and you will lose your ability to work.

DR. COX: Because I just wanted to be very specific about this because there are several reasons not to do it. But you're saying in addition to the unwieldiness with very large samples, there's a scientific reason. So my final question on this is what's a very large
DR. KING: The interfamily studies, clearly we have an opt-in strategy, right? In our New York breast cancer study, we have an opt-in strategy. I think the...one draws the line depending basically on how much time one has before the issue becomes either devastating to the world, as in the case of AIDS, or moot as in the case of tamoxifen and breast cancer. Any amount of money that one has to do triple follow-up through the various ways through mail, telephone, and personal visits of the people who don't send back cards. It is a very expensive thing to do a full-scale follow-up study. I mean it would be millions of dollars for a sample this large. So I can't give you a number that would apply to all studies. But I can tell you for the New York breast cancer study, numbers don't work, David, because it depends on where you are.

-The New York breast cancer study, because that involves so much activity on the part of the participant, that is, if she wishes to know her results she has to go to pretest counseling and genotyping and post-test counseling. I am sure we are getting much, well we're getting a 60 to 70 percent assent to be in that study. I am concerned that the people we're losing are not random. I'm concerned that we're losing the elderly women, I know we are. I'm concerned that we may be losing people who have less family history. But I don't know any other way around it. So you have to use your brains; it's a balance of the scientific questions you're asking, the money you have to spend on it, the time you have to spend on it, and the actual risk to the real person that's involved.

DR. COX: That's very helpful, thank you.

DR. SHAPIRO: We have three or four commissioners who want to speak, and then we're going to have to move on to our next subject I'm afraid. But the four I have are Bette, Larry, Alta, and Bernie. And Diane, you want a last question also?

MS. KRAMER: Thank you very much for your presentation. I sit here as a public member and I've spoken with a couple of the other Commissioners informally earlier today because as I sat here this morning and I listened to the conversation, I have this very, very real concern that we are working so hard to eliminate risk from the research activity that we may be inviting an enormous cost to research activity and to what it promises for the public. And when we had mini-hearings back several months ago, we heard consistently from the people who participated that they, insofar as they represented the general public, that they were not really concerned about this. They were only concerned to the extent that they didn't want their insurance companies to get that
information. But aside from that, they had a commitment to the idea of research, they had a commitment to the notion that there's a public responsibility to participate since the public was going to be the beneficiary of the research. I'm curious, I have a couple of questions. In working with either the people who participated in your study or the advisory group, what kind of feedback did you get from them? Did you find that they, in fact, were worried about this? Or did you find that in fact that you who were doing the study were more concerned than they were?

And do you, in the last analysis, do you have anything to suggest to us that could help us as we try to strike a proper balance between protection and permission for the research to go forward?

DR. KING: My experience in all of my work, across all studies, not just these three, has been exactly the same as yours. This is all my breast cancer work. Participants have been very committed to the work, and participant advisory boards have been very committed to the work. They make remarks that are anywhere from slightly patronizing to quite caustic about the degree that we obsess over these things. I mean someone said, "Our tax dollars at work again?" Someone else said, "How many angels do you want to put on the heads on pins?" Somebody else said, "Wake me when it's over." However it's true that they see only one part of it, and they don't see the whole picture as you do. Surrogacy instead of opting out, let alone opting in, would be an enormous help. I honestly think opting in would kill the field. Opting out we can tolerate but it has costs, both financial and otherwise. Losing the ability to follow up has, as several of us have now said, has enormous medical and scientific costs. And if there is a way that we can maintain our ability to obtain critical follow-up information on people in large cohorts, it would be a tremendous help.

MS. CHARO: I find myself wondering a couple of things here. First, by destroying the links you actually eliminated the requirement to obtain even an opt-out. At that point you could have used the stuff with impunity, saved yourself the statistical challenges that David has described, and yet you chose not to, and I'm curious as to why. Second is, in light of your experience and your certainty that opting out is far... to allow you to use their stuff in the future, either with no further consenting process or with an opting out process, in other words allowing people to prospectively contract with you for a less onerous consenting process, as a way around this problem, at least prospectively.
DR. KING: Right. The prospective studies I'm involved with use very much what you described there at the end, a process in which the ... for example, we're working with the cohort from Kaiser of young adults with inherited...with a hearing loss, and we want to find out if it's inherited or not, and at this point we have no idea whether it will be or not, so it's going to be years in the future before we know. And it has this kind of tiered system.

To be blunt, the reason why we went through more hoops than seem reasonable is because there's a lot of confusion out there, there's a lot of concern out there that if we had not gone through all these hoops that the study would have to be shut down at some time in the future. The concern is in part from our colleagues who work inside the government and who are trying to do the best they can in a very uncertain situation. It's...I can't defend the logic of what we did. I can simply tell you that our goal is to try to get to women good information and not to be completely paralyzed in getting good information to them. And there were enough people, both from the intramural NCI and among us who were concerned that if we didn't do this in the most constrained way possible that we might have to shut the whole thing down later on. Your logic is indisputable.

DR. LO: Well, I'm still trying to understand this enormously complicated dilemma that you're facing. It seems to me there are a couple issues we haven't highlighted yet. One is the sort of rapidly changing HMO field. So when consent was first obtained in the Boston study, you asked for permission to use biological markers because that's...you didn't really know what they know. And one of the things we're going to have to deal with is samples that some consent was gotten in a meaningful way but you couldn't have anticipated what you were going to use it for. And somehow, is that different than samples where no consent was obtained or only general consent to sort of use it for research? I think we need to think about the grandparenting clause for samples where, you know, an honest attempt was made to get 1994-level detailed consent.

DR. KING: If you write in Shakespearean English, you shouldn't be precluded from now speaking about it in modern English.

DR. LO: Right. The second issue has to do with an appeals process, that you were faced with a situation, it seems to me, that what is behind the original CFR regs wasn't going to anticipate it. And rather than be forced into the situation of having as a matter of prudence to take the most conservative interpretation, it would have been desirable to have some working body that could have said, let's look at your situation as a special case.
and see if, notwithstanding what the regulations say how they were interpreted, they really shouldn't apply to this situation because it's a different ethical situation.

And I guess I'm trying to find ways, because this is going to come up again no matter what this Commission recommends or what gets adopted as policy, whatever is 1998 standard consent for future uses, someone's going to come up with something next year or the year after that we really didn't specifically ask for. And are we going to face this problem again later where people are going to get a new type of study that has different risks and benefits and people will say, well you didn't really ask about that, you asked in such a vague way that who knows what this means.

DR. KING: I like your idea of an appeals process, and the woman who spoke just before lunch representing IRBs the world around might well have ... she and her organization might well have something to contribute to how to set up an ongoing appeals panel. It would have been a big help for us in this situation had something like that been in place.

DR. SCOTT-JONES: I would like to have you say a little bit more about what you're calling "opting in" as a process in your, what I thought was a very strong statement that opting in will kill the field. I was very impressed by your concern about the Jewish community and efforts that you're making to have ties with them, which I think is wonderful to have an ongoing relationship with the population, the community, that you're studying. But it seems that opting in, well what you're calling "opting out" is like what's called passive consent in some other research areas. And that is that you don't actually consent, you just ask people to respond if they don't want to participate in the research. And, of course, it isn't actually consent because you never document that the persons are giving you their agreement ahead of time.

DR. KING: Bear in mind that my discussion pertained to a situation in which a person had given a sample for whose use she had already consented. Right, specifically to that situation. When we begin new studies, they are all opt-in. Right. We are talking about in the tamoxofin case, a situation in which all participants, or virtually all participants, gave a blood sample five to eight years ago it has to be at least five because four years ago VSRA-1 was cloned—and they said, "Yes, you may use this blood sample for biological markers." But because the word genes was not used, BRCA-1 and 2, this ... all this other concern arose.
So these people have already consented, the materials are stored, so it's, as Alta would say, the second step in a process where original consent was obtained. But the question was how does that consent apply to this second situation.

D.R. SCOTT-JONES: Okay, so your statement, "opting in will kill the field" was not meant more generally?

D.R. KING: It was meant to apply to the situation in which there are stored materials, which were... which are going to be used anonymously, and which were obtained for reasons which in the context of the historic time made perfectly good sense.

M.S. CHARO: I'm now... I just want to make sure I understand your answer. The... let me just run a couple of scenarios by you and ask you which ones you're referring to - this may be the easiest way for me to get it straight. You've got a lot of samples that were originally collected in an explicitly-research context in which people said, yes you may do research on my samples. And the problem is that the research that was envisioned at that time does not encompass today's research, and so you're faced with what should I do to go back for a new stage of research: opt in or opt out or nothing. And I'm assuming that ideally you would like to be able to retain the linkages, get the best scientific work out of this. And here your claim would be that an opt-in strategy would kill this area of research.

D.R. KING: Thinking in terms of large cohort studies, yes. Assuming that we want to retain the links, if we are...

M.S. CHARO: Right, right, of course. If you don't retain the links actually you don't need to be doing any of this stuff.

D.R. KING: I need to take that on a little sign home with me.

D.R. COX: We're going to have it on a plaque.

D.R. SHAPIRO: David's been busy tattooing things on people's bodies all day long here.

M.S. CHARO: You've got a bunch of samples that were collected-not in a research context, they were collected in a clinical context. They are sitting in all sorts of path labs, and you would like to access these. It will be the first time these people are ever being
contacted about the possibility of being research subjects. You would like to retain the links in order to maintain highest degree of scientific importance for your work. Are you saying that an opt-in strategy cannot be tolerated here either, because of its cost to science?

D R. K I N G: Those weren't the questions I was addressing because it doesn't happen to be the one I'm up against. But I believe it is true. Let me say it in a slightly different way, and that is that I think that the number of important studies that could be done will be drastically reduced if that scenario is precluded, if everyone whose biopsy or pathology specimen now sits at U C S F must be contacted individually before that specimen with concomitant follow-up data for the future can be used for a study. How, what would I personally do in a real situation? I would have to confront the real situation and decide, because typically we use these anonymously and we don't try to follow up. I've belabored this already. But there will be enormous medical costs if we cannot use follow-up information in those scenarios.

M S. C H A R O: And one last thing, because we were talking earlier about economics and practicability, etc., and now, I don't know, many of you may have had the experience I've had recently, I changed phone companies. And that means that I have now seen exactly what money can buy in terms of constant re-contact. And I'm wondering if you now, anybody who's been through this knows what I'm talking about, right? If this were considered a serious concern, if the kind of effort was put into going back to the people whose samples are currently in collections around the country and getting prospective, general, or layered consent that would obviate these problems in the future with appropriate incentive, like the ones that ATT, M C I, and Sprint keep offering me, keep upping the ante on, right, would you think it's money well spent? Or do you think that this is really just not important enough that the risks are not great enough that this is an overly protective stance that we are taking?

D R. K I N G: It think that would be an enormous waste of money. And I think it would even be more negative than that. I think it would carry out the specter of Big Brother to an extent that you wouldn't have anticipated, that people would have said, how on earth did you find me, what are you doing following me around? You've got my specimen, goodness sakes, why don't you just use it, why are you haunting me, why are
following me? I think we have to recognize that there are downsides to invading people's privacy, and I would consider it, from my case, I had a lot of surgery when I was a little kid, if somebody got back in touch with me and said, we now know where you have been all these years, we have found you and we want to know about this specimen and can we use it, my first reaction would not be, sure you could use my specimen, although that doesn't bother me if they use my specimen. But it would be what are you doing tracking me down? So I mean Big Brother cuts both ways. Big Brother can be paternalistic and it can still be aggravating to be followed by Big Brother. And I'm speaking now not as a geneticist, just as a person who was a kid with a lot of surgery, you know.

D.R. SHAPIRO: Okay, well thank you very much. I really appreciate very much your coming here, it's been very fascinating to have this discussion with you; I wish we could spend more time. Unfortunately we have to get on with parts of our agenda. Thank you very much for coming. Thank you. Let me tell you the good news and the bad news. The good news is we're going to take a five-minute break; the bad news is by the time you come back you should have read page 3 and 4 of this memo so we can help Jim get that discussion started, which is really a critical... It's the, excuse me, it's the backbone of the capacity report. But the items on the next two pages will be quite important, and we talked around them for a long time, so if we can come back in five or ten minutes having read, or reread as the case may be, that part would be very helpful. Is that all right, Jim?

D.R. CHILDRESS: That's right, and we will pick up where we left off because there are still some comments on page 2 at the bottom. And we'll also have to pick up an earlier one we omitted. I don't know whether Laurie's going to be joining us or not.

HAROLD: Okay, let's get going. There are still one or two Commissioners who will join us in a few moments, but why don't we begin. Let me turn the chair over to Jim to pick up our conversation of late morning.

D.R. CHILDRESS: All right, if we could return to the bottom of page 2, and pick up the recommendation number two that we were discussion from pages 161-162, and think about how to formulate what we want to say if we've not been able to do so. And I'll just make one comment again and then I know that Bernie and Alta both want to get in on this. In fact, you had your hands up before we took the break this morning. This is the question that...basically I had a chance to talk with Jonathan and someone else since the session this morning. It does seem to me that we have two sorts of concerns.
One concern is, again, that we not exploit a particular group or class as those with mental disorders that affect or may affect decisionmaking capacity, by targeting them in a research protocol that could be done as well with some other group. And that's basically a nonexploitation requirement of a principle of justice. But we also have another concern and that is that individuals who have mental disorders that may affect their decisionmaking capacity not be excluded from protocols that, just because they have those conditions, particularly, for instance, if they could give consent. So...and some of those may be valuable to them as members of the group or individuals with particular conditions. So the critical question is how we state this and whether we want to change what we've written in a way to clarify the points we want to make. Bernie, do you want to get on this now?

DR. LO: I'll pass.

DR. SHAPIRO: My view of this is that if it is a study related to mental disorder from which they are suffering, such as the example of Larry in proposals and text here, then I don't see...there's certainly no reason to exclude them, every reason to include them under appropriate circumstances and so on. That's not an issue, I think, although we discussed it, we all agree with that. Then there's a second question of whether what...what is said here, research that is indirectly related to their mental disorder. I don't know quite what that means, but if it means it has some but not very direct relationship, if that's what it means, then I would come down the same place.

I would favor under appropriate circumstances that they be included. If it bears no relation, or no known relation to their mental disorder, to me it seems that the benefit of having them be able to participate if they consent are outweighed by my other concern, maybe that we not be in a position of taking advantage of this group. If it could be as easily and as well done in other groups, I'm a little worried about that.

DR. CHILDRESS: That's as a group because we think, again, the individual who may want to enter a chemotherapy protocol for cancer, who has a mental disorder that may affect decisionmaking capacity, but who knows that? It seems to me that at that point we're treating them not as a member of a group of those with mental disorders but rather as...is the protocol can be done with, and is being done with the general population, then it seems to me that a person who has a mental disorder that may affect decisionmaking capacity can give consent. That's why I distinguish targeting those with mental disorders as a population or group or protocol, and that I think is ruling out, unless it really is necessary to do with that population, versus a study that is being done with the general
population for which a particular individual with mental disorders that may affect decisionmaking capacity might benefit.

DR. SHAPIRO: I agree. It's hard to distinguish the individual level from the group level.

DR. MORENO: In that spirit, Jim, maybe we should replace the word "involving" with the word "targeting" in the statement that appears on page 162. "An IRB should not approve research targeting, or may not approve research targeting subjects with mental disorders," etc.

DR. CHILDRESS: All right, there were several hands. Trish.

MS. BACKLAR: I'm actually going to repeat what I said when we broke off...what if you have somebody who has a bipolar disease and cancer and is perfectly capable of making a decision about involving herself or himself in a cancer study? Mary Claire's study or whatever?

DR. CHILDRESS: We would also actually permit such a person being involved even without his or her consent. In a therapeutic trial.

MS. CHARO: If I'm understanding correctly, what Jonathan is suggesting is that the language make it clear that what you could not do is target people with bipolar disorder in order to recruit them primarily or specifically into this study. But if one happens to respond to a general recruitment call and is capable of consent, there's no problem.

DR. MORENO: Right, that's the spirit of it anyway, Alta.

DR. CHILDRESS: Is this direction one that we think is workable?

MS. BACKLAR: And of course at the same time we want to make sure that people are not being recruited into a study just because they're mentally ill and they could be easily used in a study which has nothing to do with their illness.

DR. SHAPIRO: That's what the target, I think, is supposed to mean.

DR. CHILDRESS: Right.

DR. COX: No, I really think that to be so paternalistic, because someone falls in this class, to abrogate their options as an individual, is just too much. I mean, it's too
much to handle. So, I think that's one of the points that Laurie was trying to make about this, so we have to really maintain the individual's right to choose. If we take that away in terms of protecting them, then what are we doing?

DR. CHILDRESS: Other points, Bernie?

DR. LO: Yes, I just would like to suggest that the explanation that you gave, Jim, about four minutes ago be incorporated so that it really clarifies things.

DR. CHILDRESS: Okay, other points on this one? All right, if not, let's turn now to...let's actually go back and pick up the first page and the second bullet because it's closely connected to the one at the top of page three, and that is whether we're going to stay with two categories of risk, whether we want to go in the direction of three. So let's deal with that question first, the two categories of risk versus three. And then well see how this works out on the top of page three. So, back on page one, two categories of risk...Alta?

MS. CHARO: Jim, especially in light of Mary Claire King's presentation, which gave us what Eric Meslin calls a boundary case, that is a kind of example of exactly what might be lost if the regulations that exist or that are being proposed can't accommodate it, I feel like in this area of two categories of risk where the second category prohibits research to a large degree if consent can't be obtained, with very few exceptions, that it might be very illuminating to find out what would be lost. And although I'm hoping in the public reaction that we're going to get some proposals about what might be lost, it also occurred to me that we might find out a little bit by looking backwards. If we were to have on our staff or by a contractor somebody go to a few of the most prominent journals in these fields for the last 20 years and just take a sample of some of the publications and the studies that are described there, and ask for the methodology of each study, could it be done under the rules that we're proposing, and help us understand which ones couldn't have been done so we'd have a very concrete idea of what would have been lost had the things we're proposing today been adopted 20 years ago. It might help us to understand exactly what the quid pro quo here is for the protection of subjects that up until now has been adopted as the view of the majority of the Commissioners, although not without Laurie Flynn's dissent. I would find that helpful in getting confident in my own judgment.

DR. CHILDRESS: I think that's a very good point, and let's say if others want to
comment on it. Bernie.

D R. L O: I agree, that you've been concerned at the way a lot of research which is maybe not a whole lot more than minimal risk will be for all intents and purposes virtually impossible to carry out. And I guess I would be more forward-looking and go to reputable, thoughtful, sensitive, investigators who care about patients and not harming them, and say what types of pivotal studies would be either precluded or virtually impossible to carry out if Appendix 2 were really implemented?

D R. C H I L D R E S S: We could provide a summary of our recommendations and the flow chart and actually get feedback. Eric, and then I have some other comments.

D R. M E S L I N: Just as a reminder, the purpose of the public comment, period, is twofold. One, the document is out on the Web, was placed there last week, and as a reminder, we sent over a hundred letters with copies of the report, the entire report, to individuals, both of the kind that Bernie has described and individuals reflecting advocacy organizations, patients' organizations, researchers what we felt was a broad cross-section of the community. And the letter, a copy of which is in your briefing book in advance of this section, which describes what we were asking for. I hope...gets to some of these issues. We did not specifically ask the question that Alta has, I think, quite appropriately raised, what would be lost if the document that you now have in front of you were implemented tomorrow. But we're hoping that by reading through that letter that that kind of message will come through. In the event that it doesn't, we do have the luxury of continuing that process. And the second point is just to remind about the protocol and consent form review which won't go back 20 years. It will only be going back at this point to 1995, and that will give us at least a sense on the permission side as to what research looks like now or has looked like over the last few years. So, not exactly what you're asking for, Bernie, but that solicitation was intended to elicit some of those points.

M S. C H A R O: I'm hoping we get all that, and I will value it tremendously. I'm suggesting a retrospective look as well for a very specific reason. My experience, my limited experience, has been that under some circumstances people in the scientific community will promise the moon. When they need money or they offer restrictions they'll talk about all the great things that will happen. And then when somebody worries about the consequences of all this, then they'll say "oh, it's not really going to happen" or
"it's really decades away." I mean that's just a human tendency. And by doing a retrospective, you get away from speculation about what would be lost and what the conditions of research would be in terms of the harms or the fears or the discomforts that would be suffered by the subjects. You can actually look in a more concrete way at actually what precisely would have been lost and what exactly was the experience of those subjects who might have been enrolled without having been able to adequately excuse themselves from the research. So, I'm still kind of interested in doing this if it's not too unwieldy, which it may well be.

DR. MORENO: I think the results of such a sampling would be interesting. However, we know in advance that there is only one set of circumstances in which studies that may have been done would be precluded under these recommendations without Secretarial approval. And that is greater than the minimal risk, no benefit studies, without informed consent. Now that...either that is a very small universe and/or it is universe that most people on the Commission, I gather, would not prefer to see continue anyway.

MS. CHARO: But this is the place where the two categories thing becomes crucial because the question would be, Would some of the things that we would have lost been retained under a rule that had a slight increment over minimal risk third category? In other words, a kind of test of the effect of having a third category.

DR. MORENO: Yes. What concerns me, of course, and I know you've thought about this too, is how we assess what counts as falling into greater than or a little more or a lot more. And that's why I am somewhat concerned that the information that might be available with a lot of effort from such an investigation may be minimal.

DR. LO: You know, again, I think what I most need is a real-life example. I mean it's one thing in the abstract think that we may be missing some important...we may be precluding some important research. And some like Mary Claire King say, let me tell you about a study, let me tell you how we tried our best to make it work, and why we decided to do it in a way that very clearly, I think, compromises extremely valuable knowledge, that's really important. So I can't tell what the size of this box is until I hear some real examples. I think it's very hard to do this abstractly without thinking of some specific studies in mind. And that's why I think we need some help with it.

DR. CHILDRESS: Before I get Diane and Trish, would it be possible to select a
dozen or so of the people to whom have already written and say, look, we've had this particular concern? We know it really doesn't matter, in many ways it's a biased group, because what we're really interested in is can you identify some studies that are really important, that would not be...that could not be done under our framework.

And actually it's important to have those who would be most suspicious of our recommendations look at that. To show us the studies, and if we could find that then that would actually be helpful to us, I think. Would that be a plausible way to proceed? See any reason not to do that?

DR. COX: We need to remember though, that they could not have been done with this kind of subject. Many studies have...the way the brain lights up under various conditions can be done with other subjects.

DR. MIIKE: Can I ask a point of clarification? If we have a third category, what are the additional conditions that we would impose on it compared to the two categories that we have now?

MS. CHARO: It's hard to see what the value is if it increases the number of categories.

DR. SHAPIRO: I agree with that.

MS. CHARO: You might accomplish the same thing just by allowing some of the procedures to be placed in the minimal risk category. I think when you start with ill-defined, fuzzy categories like slight increment over minimal risk, you step out on the slippery slope that might allow you to infinitely increase the categories when you wanted to allow more research to be done with fewer restrictions. If we could categorize procedures or techniques as risky or involving only minimal risk or no risk, I wouldn't see what the category would be.

DR. CHILDRESS: One problem with that is that there already is a set of regulations and tradition of interpretation of minimal risk versus more than greater minimal risk and so we have to be able to tie into those. We can't simply say well, this procedure you want to do, this as minimal risk. It seems to me that that's going to end up with a similar set of problems. Trish?

MS. BACKLAR: As I'm listening to this, I'm worried that we're going to go down the slippery slope of the human genome of the human biological material report. And that we're going to get terribly slowed down. But I think that one of the things that's
extremely difficult here, and in all of these reports, is that when we identify these things we do it in a sense with thick fingers, and the cases themselves are going to explain themselves so the research protocol will give us, or hopefully give the reviewers some better idea of where it will fit.

Also, the aspect of this which is so very difficult and from the very beginning we've known that is that we are identifying a population which is very buried. And what may be minimal risk for some members of this population and not for others will be altered by what their particular disease category may be.

M. S. CHARO: I've been an advocate of keeping the two category regime with a highly protective standard for the greater than minimal risk category all along. But I'm still searching for something that will help me be confident in that judgment. Now, we have a model for a three-tiered system in the area of research with children in which they do use this intermediate category and in which they have a three-tiered protectionist scheme. I wonder if it would be possible to supplement the letters that have been sent already, perhaps, with a smattering of letters to perhaps the chairs of IRBs around the country, at children's hospitals perhaps, as well as at a couple places that don't have a large pediatric population asking them about their experience in applying a three-tiered system for children's research, how hard has it been to be confident in their own judgments about what belongs in what categories. This would be a prelude to, Larry, worrying about what should belong in each of these three categories as far as protective measures should we decide to backtrack and move toward a three-tiered system. But one of the objections to a three-tiered system has been that it can be unwieldy, complicated, difficult to enforce, etc. And maybe some feedback on the one example we have out there would be helpful.

D. R. LO: I think this discussion needs to tie in with the discussion of what's in the boxes on the bottom level. So one of my concerns is not so much with the yes/no dichotomy as to what the implications of being in the no column now as I read down the page. Again, I think in our draft I don't think we give a convincing explanation of why we chose what is contained in these two boxes. So although it certainly makes sense to be more stringent for the no rather than the yes in terms of unable to give informed consent under the no direct benefit, greater than minimal risk, why are we going to prohibit it without Secretarial approval and not some other set of protections that are less stringent than that? So part of it is sort of what the implications are being in the sort of most restrictive set of shoeboxes.
DR. CHILDRESS: And I think that really is not spelled out clearly in the text. I think the Secretary aside, wouldn't you agree, Jonathan, that something we would need if we're going to keep that to really work up further, and that obviously is the connecting question on page 3, that's connected to the one we're just dealing with. Let's see if there's anything else you want to say about the proposal out on the table about how we might get some additional information out. Eric, then Jonathan, then there was a hand here.

DR. MESLIN: I was just going to make a proposal on behalf of staff, if that would be helpful, which uses Alta's suggestion. We can both contact directly individuals to whom we have already sent letters and ask them to provide us with some specific examples. I think phone conversations might be a helpful way of emphasizing our interest. We have, as I say, 114 folks. I can assure the Commission that probably 15 or 20 at the very least would be delighted to provide us with some specific case examples of the kind that Alta is describing, plus or minus the IRB Chair idea. I think the idea of the two or three categories in IRB Chairs being asked for their experience can also be done through either a telephone solicitation or a letter solicitation. Jonathan was going to interrupt me, sorry.

DR. MORENO: Sorry. But I think the critical question surely is not how hard or easy has it been for IRBs to use the three boxes for kids. The critical question is how appropriate have those choices been. And I have some doubts, speaking professionally, about how appropriate some of those choices have been. I think the methodology will not get to that. The only way to do that is to convene a subcommittee, a super-IRB, to look retrospectively and reevaluate some of those judgments. I think to get a meaty result from this aspect of what you're suggesting is going to be harder than just asking IRB Chairs to respond in a simple fashion.

DR. SCOTT-JONES: I would just like to again try to make a case for the two categories over the three. I think that when you put any study into categories, whether two or three, you could always possibly make a ranking of those experiments or studies within the category and claim that some are more risky than others. So you will never create a situation where when you use the categories you have a homogenous grouping of studies within the categories. So I think it's futile to try and create another category so that you're always putting in those categories studies that are at the same level of risk. That just isn't the way studies will be. Studies will be very diverse, they'll be very different. So I think there's futility in this effort to resolve a problem by creating categories. I think
the way you resolve it is really by having the investigators and IRBs, anyone who's in a position to comment on the work, be very careful in how you go about assessing risk because that's something that's very difficult to do. And I think that's where the energy needs to be placed, not in the number of categories that one uses. Three categories isn't superior to two when you have a very difficult decision and you're still going to have a lot of variability that's more than three points.

DR. CHILDRESS: Before we get Harold in, let me just...as I understand sort of the direction we've gone from Alta, and I hope I don't misinterpret you here, it's something I share hearing the previous conversation, namely, not that we're calling into question the two categories. What we want to do is get the best information we can to test those categories before our final report. We heard some things in the previous discussion that at least might cast light on some of the issues and the genetics of stored tissues, now we'll report a little different way. What we'd like to know are there some cases like that that would pose problems for us here. So it's not so much that we're challenging the two tier but really sort of testing it to see if we have actually been able to want to. Is that the direction you were going, Alta? I just wanted to share that.

MS. CHARO: Absolutely, Jonathan has impressed me with how difficult a task it will be, and I simply commend the staff with the task of seeing if it's possible.

DR. CHILDRESS: It's possible.

MS. CHARO: It may not be, but if it's possible to get anything useful.

DR. SHAPIRO: Can I make a comment about this? This is not...I don't think we should think about this as whether we like two or three or even asking the question which couldn't go ahead with two or three, which incidentally is impossible to answer, unless you know what level of protections are you going to put within each category. Now if we distinguish three, but two of them have the same level of protections, it's totally irrelevant to the question. So...the question we've been talking about, then, is not well-defined.

And so I think if I could suggest that if we go ahead of it and then see what protections come along the bottom line here. Then ask ourselves the question, if something were a minimal increase over, excuse me, whatever the terminology, a small increase over minimal risk, would the protections vary at all? If the answer is no, then the whole study's not necessary. And so if we get to that point, maybe we again can circle back here and see if we have a well-defined question to ask. And as I look at it, if you look at the diagram,
which is the simplest thing to look at to get a quick look, what Bernie's been referring to, it's on 173, and ask yourself all right, if there were a small increase over minimal risk, would it need any boxes here or just leave the same old boxes. That's exactly what we found out, incidentally, when we got bogged down in the biological materials. We had all these different boxes and they all mounted to the same thing.

M.S. CHARO: But the answer here is actually that there would be a difference, and this is what Laurie has been so upset about, that if we had...

DR. SHAPIRO: Only if we say there will be a difference. We have to decide that.

M.S. CHARO: Now we're moving into the land of totality, of course, but this is the essence of her objections. She would like to have possibility of some kind of surrogate consent process or nontherapeutic studies that are only a minor increment over minimal risk. And that would be the new category. A full panoply of all the protections, all the other stuff might...

DR. SHAPIRO: That's right, it would be if you looked down at our diagram or something, it's that it could get into the box that's second from the left.

M.S. CHARO: Essentially nontherapeutic, minor increment over minimal risk would be treated the way we now treat therapeutic greater than minimal risk. It would move this small group of nontherapeutic studies into a regime of protectiveness akin to what we now use for therapeutic but risky studies. And that's what she would like to have done, and that's where this fight has been focused. I think.

M.S. BACKLAR: I think it's helpful to get out of the boxes for a minute and to go back to the reasoning that we originally were talking about-why we saw it as minimal risk or not minimal risk. And that was because we looked at many members of this population, even in minimal risk studies. I just have to use as an example my own studies in which it's clearly minimal risk in which there are certain things that can obtain that I would, even in this study, be concerned about if I had someone in the study and I did not have an outside provider for them in case something went wrong. Not even during the interviews, but for instance because the person was upset about something that occurred in the interview. Now we've already agreed, you don't need to have all these things in place for minimal risk. Right? And so knowing that even in studies which were minimal risk, there is risk for many people in this population. I don't know what
differences you would make with a third group. Am I making sense?

M S. C H A R O : All my understanding of Laurie was that she would want the same protections for therapeutic but risky research to apply to nontherapeutic, only a minor increase over minimal risk research. So that would give you the answer of what those protective measures would be.

D R. L O : Let me try to take a different tack, which is to offer an example of the study that I'm concerned about landing in the "prohibited without special Secretarial approval" category. So I'm going to try and develop a scenario for a study which is more than minimal risk, of no therapeutic, no potential direct benefit to subjects, and the subjects are unlikely to be capable of giving informed consent. Okay, and that's a study where you pick your disorder X severe schizophrenia, severe bipolar disease X and the aim of the study is to try and correlate, just to test an association between results on imaging studies and levels of neurotransmitters in the brain. And the goal of the study is to try and find surrogate endpoints for screening candidate new therapies so that you can more effectively screen out candidate new drugs. And I think it fits with the notion that there's going to be a lot clearer design of drugs and a lot more candidate drugs and they want to test them more efficiently, to throw out the ones that aren't going to be of benefit. So the goal would be to try to develop surrogate markers by using imaging studies where you could identify drugs and new therapies that might be potentially beneficial.

So I'm trying to construct a case that although it's not directly beneficial, it provides basic knowledge of the pathophysiology of the person's condition, which could then lead to therapy. So I'm trying to understand the concepts that underlie some of the boxes in the children's research thing. We've already said that certainly a lot of our puncture and also MRI studies are more than minimal risk for this population. And I guess I would like to argue that to make those studies acceptable only with special Secretarial approval basically means you're not going to do the studies, realistically. And I'd like to say is there something short of that that involves surrogate consent, prior research office directions when they're in remission, no apparent dissent, health care advisor.... But is there any sentiment that, for those clients who have started, are people willing to have some other box that's filled with something other than just "prohibited without special Secretarial approval"? And I don't know if that's the stone answer I'd like to get. You know people are in the field to help construct a scenario but it seems to me that there may well be studies where we'd want to have more protection than is now available but something not
quite as stringent as Secretarial approval.

DR. CHILDRESS: Just pick up on part of that before we get others in...if you could, for instance, get the advanced planning as sort of discussed here which your example seemed to suggest, and that would actually pull it over in the category of "yes" in terms of capable of giving consent. That is, if a person would have a period where a person could engage in advance planning, that is actually included as a possibility.

DR. LO: But you're saying it would be under the left column.

DR. MORENO: Yes, it would fit. So that would be taken care of, but there may be other, even beyond that, there may be other situations where you might be proposing other kinds of ....

DR. LO: Jim, but this was not direct benefit to subject.

DR. CHILDRESS: That's right. So that would be included.

DR. MORENO: If they could do advance planning, the other alternative that I've heard some people talk about advocating is using less affected subjects in the beginning, try to develop strategies that are more likely to be beneficial, and again in that box the subsequent studies.

DR. LO: But the box doesn't reflect that though.

DR. CHILDRESS: ...it includes it. If you look at 154 for example, page 154, it's included. But the box doesn't clearly capture that. That's one of the shortcomings of the box, but it's in the text.

DR. MESLIN: It's 154, lines 3 to 5 in the text, which I don't think are captured in the boxes of 173. And the sentence reads, "As is the case for studies that present a potential direct benefit", and this is still under the category of no direct benefit, "their consent to a particular study may be obtained in advance of a period of incapacity." That line which I just read on 154 is included under the section, "greater than minimal risk for research that is not potentially beneficial to subjects." And the appendix does not actually have a box. An error in the appendix we've got, an omission, I'm sorry.

MS. BACKLAR: And there is something here that I'm concerned about in this box that we have where it doesn't offer potential benefit, the box that Bernie has been looking at. And you get down, "Are subjects likely to be capable of giving informed consent." Now I've lost the box where we were looking...that's the box...so if they're likely
to be able to give informed consent, well then there is much less problem, right? And so what is the ... I'm not quite certain what you're concerned about.

D R. L O: W ell, it's the difference between giving informed consent at the time you're actually going to do the procedure, and giving the informed consent in remission when you're eligible for the study because that's not what the study's about.

D R. C HILDRESS: And so what we're saying is the box doesn't match the text, and the text does include possibility of advanced planning.

M S. B A C K L A R: But that is then what concerns me. I want to make sure that that advance planning is always for a particular study.

D R. M O R E N O : T he text also does say that.

M S. B A C K L A R: I don't want to see that kind of blanket. I'm saying it's okay to anything.

D R. M O R E N O : I t's not a blank check, it's a particular study.

M S. B A C K L A R: O k ay, that's what I ... just wanted to verify that.

D R. M O R E N O : T he text shows that.

D R. C HILDRESS: O ther points on this? There's...Bernie, do you, excuse me, there may be other aspects you're concerned about as well.

D R. L O : A gain, there are different types of advance directives, and some are more to specific than others. If we're saying you may only give an advance directive to one specific protocol, we're going to run into the same troubles that Mary Claire King told us about with, say dementia, where you give one crack you're giving your consent, two years later there's something else which is very comparable to what you've consented for but you're saying but no, you didn't specifically consent to that so we can't do it. So I'm a little...I mean I don't want a blanket consent to anything. But it seems to me that if I want to consent when I'm demented to imaging studies that, as best as people can tell, create the risk of anxiety and minor irritation from getting an IV put in, if there's a new type of imaging study that isn't a PET scan and I didn't consent to it, I'm a little concerned of someone saying well, you didn't consent to this specific thing so you can't do it. Where capacity is fluctuating, you can always go back. But you know, all the research on Alzheimer's you can't do.

D R. S C O T T - J O N E S: C ould I just ask a question following up on what Bernie's
saying? Bernie, I guess it's not clear to me, why would you want the person to be in one study and then another and then another?

D R. L O : No, no, I'm not saying one study, then another, then another. But I'm saying...it's a different issue, but if I'm saying prospective consent and by the time I'm eligible for the study, it's a different protocol, it's a different generation scanner, different type of scan, or something. I mean how precise do I have to be in a degenerative condition. I'm not saying use me for every single study that comes along. And you can say you only get to be in one of these studies.

D R. M I I K E : I don't think that's our notion on what consent is. I thought that we're talking about consent very close to the onset of a particular study. So you're talking more like an advance directive like....

D R. L O : Yes, I'd be interested in it but they're spreading the research apart. I don't think we've ever considered that as a consent, right?

D R. S H A P I R O : Bernie, is it tough at all to observe, maybe there's just diversion for which I apologize, that if two new generations' ideas and procedures come along, as was presented to you this afternoon. And in lots of cases, unfortunately new generations of potential subjects come along. And therefore you don't ... now there was a very special case here because they want to follow pedigrees over a long period of time and that was a very special, important case. I don't know, I just ask that question now, I don't know whether there are analogous cases for these kinds of procedures or not. I just don't know enough about the ideology of the diseases and so on.

D R. M O R E N O : Some of you have heard my take on this issue before. In general, my view is that our society has not endorsed a notion of anybody being able to give blanket endorsement to research participation in advance-for any population. I don't know why we would want to start with a population that has instrumental disorders. I need help from the lawyers here, but I don't know any state legislation that creates a legal device that would enable me as a relatively competent person, still in spite of my work for NBAC, to authorize my use in a blanket sense 70 years from now, 50 years from now in research.

D R. L O : I guess it seems to me there's a big difference between blanket consent and consent for a more well-defined study. I mean it's the problem with advance directives. I mean if you're going to restrict it only to guessing the specific interventions of specific study, it's going to be very, very narrow.
DR. MORENO: But again in the case of traditional advance directives, at least, as a notion of therapeutic benefit, we lack that here. What we're really talking about here is giving one's body to science, while one is still alive. And that's not...my understanding is that so far we haven't discussed that question.

DR. LO: Well, I think that if, again to use the analogy from children's choices, if pathophysiology of that condition is important to study as the basis for future benefit, there is some value to wanting to do it. And also it seems to me there are different types of risks. So I think blanket consent means you can do anything. I'm saying that drawing on this notion of a little more than minimal risk seems to me there are some things that are risky but we're not talking about the kinds of side effects you get with chemotherapy or major surgery. You're talking about things which are transient, which people may not necessarily remember which are not...don't lead to further problems.

I think to put everything together and say you can't do that without Secretarial approval, I think we may be giving up a lot and I think I'll just wait and see what people in the field have to say.

DR. MIIKE: But if they can give consent it doesn't fall in that category. It's only when they're incapable of giving consent.

DR. LO: Right, right, and I'm saying that if they gave consent before but not to that exact study but something awfully, awfully close, and it's just pathophysiology, and not a whole lot more than minimal risk, are we going to say can't do it without Secretarial approval?

MS. BACKLAR: I would be terribly afraid that somebody who is eagerly doing research in an area that you would say is not so different that this would bend in ways that you might end up having people in research protocols which were far away from what they would precisely have agreed to be in. And then I think about Al Jonsen yesterday talking about how their view was shaped by Hans Jonas's view that they weren't going to have this utilitarian consequence on list balancing. And I'm concerned about the same thing here. I want to make sure that we have adequate protections for people who may not be able to protect themselves.

DR. CHILDRESS: Are there other points that should be made now, particularly about the section on page 3 and then the materials that follow? Under the heading of "Research Involving Greater than Minimal Risk that does not offer the prospect of direct benefit to subjects." We've already touched on a fair amount of this, moving from the two
categories of risk. But are there other things we need to say about this? Again, one thing we don't have in the text is a very clear explanation of the approval by the secretary. We do discuss it on page 152, I think it's some place in the text that I found it. But are there other points that you want to make about this, and then about ways to harmonize what we say in the text? Again, I think most of those can be handled in an editorial way. But Harold had recommended that people look over pages 3 and 4 particularly carefully for these related points.

DR. MIIKE: You know the top of page 3 is also related to the last point on page 4.

DR. CHILDRESS: These all four go together here. Pages 3 and 4 work together involving the point at the top, plus then how you'd work out the understanding of individuals who can consent and those who cannot, and then the last part that you know. So what do you want to say about these two pages?

DR. MIIKE: Can I comment on the last part of page 4? It seems to ... it doesn't make sense because it says, "for individuals who cannot consent," you're going to require before they even go to Secretarial approval that they would have given their consent in advance. Well but you said...you're recommending that they be changed to include both conditions. Aren't you doing that?

DR. MESLIN: They would not be jointly necessary but one could occur or not. That's a confusion in the text which we would like to clarify. But there are two places where individuals who cannot now consent could participate.

MS. CHARO: You want to be consistently A or B.

DR. MIIKE: Okay, I was reading that recommendation and I thought that you were adding the A to B.

MS. BACKLAR: We are now looking at for individuals. We skipped over this middle section that I thought we were looking at and we're looking at this now on page 4, the bottom of page 4 for individuals who cannot consent? Is that correct?

DR. CHILDRESS: That's right, it ties back to the top of page 3. Okay, we've...basically is right...we've been skipping...the middle part...it's organized in a confusing way. But this part on individuals who can consent, on the middle of page 3 to the top of page 4 really is a matter to be handled editorially. What we're really talking
about is this first paragraph on the top of page 3 and the part that Larry directed us for at the bottom of page 4, right? Those are the two connected passages and basically what we want to say about the requirement of consent for participation and research involving greater than minimal risk, that it does not offer the prospective direct benefit. And what we want to say about Secretarial approval.

D R. LO: Right. Now, Larry's question, then, I thought somebody said this box down here should read either Secretarial approval, is it an prior consent in advance of the...

M S. CHARO: Or.

D R. MIKE: No, that box is okay, Bernie, because the left side of the box would say that there was consent obtained. So it mirrors the box, it's either/or. Neither consent was obtained or consent was not obtained, Secretarial approval was.

M S. BACKLAR: Okay, okay, all right. This is not as confusing as we have made it.

M S. CHARO: All the people here who are fuzzy after meeting too long raise their hands.

D R. CHILDRESS: We're reaching the end of the day. Yes, any other points that need to be made about this. And obviously we will have to continue some of the discussion.

M S. BACKLAR: I think I need a surrogate to make some decisions for me.

D R. CHILDRESS: And need to listen very carefully to Laurie's arguments, it may well be well end up obviously with individuals filing dissents to different parts of the part after we've gone through. Are there other points that need to be made about 3, pages 3 and 4? I have just a couple other points I'd like to raise, and I'm sure other Commissioners do to about the draft and then ... other points about 3 and 4? Let me offer just a few observations. Again, I think we've made real progress on this draft, and thanks to all those who've been involved in it. One thing that I think may not have adequately reflected in our recommendations and in our special protections is something that came up, comes up in the report earlier, and something we've talked about before. And that has to do with the contextual elements that the IRB might consider. We don't bring in, for instance, consideration of institutionalized versus noninstitutionalized. Some of these contextual factors I don't think we really worked in very well even to our guidance to IRBs, and that's one thing we might try to do. Then a few other points I have
may appear to be editorial in nature but I think they're not. I think they're actually more conceptual than they are editorial, and I'd like to make them and get them out on the table because they affect the way we think about the structure of the report.

If you look at the table of contents, I feel very strongly that we ought to reverse the order of Chapter 4 and 5. Because we have Chapter 3, and I'm going to argue for retitling that, that really focuses on voluntary informed choice. And we have Chapter 5 that deals with advanced planning, surrogate decisionmaking, and the like. And we have in between those two a chapter on risk and benefit. And it seems to me that five really follows from three and that's a structural matter we ought to take care of. So it's more than editorial, it really is conceptual matter, how you can see the project. I think that connected with that that we really need to retitle Chapters 3 and 5, because we've got a criticism of the draft that focused on the fact that we don't really deal with informed consent, but actually Chapter 3 is on informed consent and the limitations of informed consent. But that's not really reflected in the title, so we need something like "Informed Consent and Limitations on Decisionmaking Capacity." Because that, first of all, what it means is you've got voluntary informed consent, and then looking at the limitations because of decisional impairment and the like. Or in Chapter 5, which I would suggest would be now Chapter 4, we need something like "Assent, Dissent, Advance Planning and Surrogate Decisionmaking" because even though you can't tell from the table of contents we have here, the whole first part of that is on assent and dissent. And that's where we bring their argument and discussion in the text about how we relate to the National Commission. I think those are...I'd like to propose those unless there are strong objections that could be taken account of when we make the next revision. Those are some of the thoughts I had, what other points would you like to raise about the draft, the recommendations, the framework of protections?

D.R. LO: I'd like to readdress the issue of IRBs. As I read through the report, it seems that one of the crucial things we're doing is asking the IRBs to play a more active role in protecting persons with possible impairments in decisionmaking capacity. We really are asking them to do a lot of different things. To put them all in one place, special scrutiny to protocols that intentionally cause harm, identifying problematic study designs, scrutinizing the procedures for evaluating decisionmaking capacity, evaluating the scientific merit of the proposal, determining which supplemental protections are warranted in particular cases.
That's a lot of responsibility. And I think I want to put that in the context of a lot of growing concern now that IRBs simply don't have the resources, and may not have the expertise to do this. And even taking into account the recommendations to add additional members and to perhaps the audit, which I'm not sure of, I think I have concerns about making so many of our recommendations hinge on a process, a technique, that is of questionable effectiveness doing what it is now supposed to do for a whole host of reasons. And I know we're planning to do a separate report that addresses that, but it seems to me that as part of this report, we need to try and address some of the fissures because frankly an IRB is not going to be able to handle this. I mean they're stretched to the limit. And unless they get a lot of extra funding to do this, I think we're not...the protections we're hoping for are not going to materialize without a very robust, active, IRB at major institutions. So I'm concerned about making the implication realistic in the real world. And there're going to be real costs, we talked earlier this day about monetary costs. I mean we're really talking about asking institutions to make a substantial commitment to our views. That's just not there now.

DR. SCOTT-JONES: Bernie, I see your point about IRBs and the fact that they're overburdened, but what would be your alternative for recommendations that we could make in this report? If we don't make the IRB central in this process, what could we do instead that would be helpful?

DR. LO: Well, I'm not sure I would quite answer it that way. I would say what do we need to say in our report to make the IRBs really capable of taking all these additional tasks. And to really explicitly spell out we understand that IRBs are being asked to do increasing amounts of work; they're dependent on volunteers; don't have enough administrative support. These are things, they may not be trained to think about some of these issues. These are the things that we suggest need to be implemented to make this really feasible.

DR. SHAPIRO: I actually have a lot of sympathy for that. I think that we should find a place in the report to acknowledge the increased burden, the increased set of requirements, and acknowledge the fact that the system as a whole has to find institutions and better support the IRBs themselves. I thought a lot about whether there is an alternative arrangement.

It's not easy to think that with an alternative arrangement that would be anywhere near as
effective. And despite all the limitations, and genuine ones that you have pointed to, I think if we can say something now about the need in this context, at least, to strengthen these institutions in various ways, that would be very helpful and then when we follow that up next year with a report that has more to say about this. So I'm sympathetic to acknowledging this and not pretending that this could be just put on their plate without any...they'll just do it. I think there's enormous variability in institutions regarding how our IRBs work, how much institutional support they get, how well organized they are and so on. But nevertheless, your point is well taken, I'm sympathetic.

M.S. BACKLAR: And there's a section in the report where that could fit in very well because you've started a section, the reason there are extra costs and why one will have to pay for this.

DR. MORENO: I had the opportunity about two months ago to present the draft recommendations to an FDA-OPRR workshop in Albuquerque. And I said at the beginning of the talk that I was afraid they wouldn't like me very much when I got to the end. These were, of course, all IRB people. And I was surprised at the benign response. Now that might be because a lot of these IRBs work with people from Native American communities who already have a high monitoring and reconsenting and so forth in place. Another case, an individual from a very large, research nurse, from a very large academic medical center, said they had already a liaison as I mentioned before who does much of what I've been talking about. And she wasn't put off at all. So this leads me to a practical suggestion. Perhaps what NBAC might want to consider is after this report comes out, is sponsoring a conference, perhaps with another organization, perhaps OPRR, where individuals from some of these institutions could model their work, could model the arrangements that they have already, and give a very practical indication of what kind of institutional vestment it has met. Because I think although many of the larger IRBs, we also knew from the Belmont Report, that about 10 percent of IRBs do 48 percent of the protocols. So there's a small number, they are very stressed. There could be a specifically identified effort to help them make the arrangements they need to make with an assessment of how much it would cost them.

M.S. CHARO: First I second the suggestion about a conference; I think it's actually a very nice way of disseminating. I'd like to perhaps even encourage us to take one step beyond what Bernie and Harold have suggested on this text. In the Executive Summary and in the Introduction to the recommendations and whatever short version comes out as well as in the main text, I'd love to see us emphasize that after much
deliberation it was only a nuanced, scaled, complex approach to a range of protections that emerged as a realistic way of managing this problem. But no other solution really seemed to present itself, and that we were perforce required to send this kind of work somewhere, and that the current system either has to be massively changed or massively improved in order to accommodate this work. And to do the same thing in the biological materials report, and to also note in both of them that the structure of human subjects protection in the federal government makes it difficult to make these changes in a regulatory fashion because of not only the decentralized IRB system, but the decentralized authority over human subjects protection in the U.S. government. And in this way truly use these reports to build a record towards next year's report on the human subjects system. Use these very deliberately to introduce some of the difficulties as inevitable unless there is change. Because we already know the system needs to be changed, it's already been stressed beyond its capacities and it's not been enough. So maybe the addition of these, which are our conclusions of what you absolutely have to have to do it right and yet is now a straw on the camel's back will be enough to perhaps get some attention to the need to change the system.

D.R. LO: I'd also like to urge us to list out some of the directions we think things need to go. And we have some of this within the report. I mean, inclusion of a meaningful number of persons who have some knowledge of their condition and how to fix potential subjects, increase in staff, particularly for like things like consent monitoring. I'd like to say, you know, for IRBs that routinely see a fair number of protocols that deal with population, there should be some mandatory training for at least some of the people in the IRB to familiarize themselves with what's in this report, and it's not just reading the report.

M.S. CHARO: I suspect that when we get the public comments back that a lot of them are going to have a kind of bifurcated look. Nifty ideas, wonderful thoughts, some of them will hate us, you know, but nifty ideas, wonderful thoughts, can't possibly be done because we need X, Y, and Z, and that we should be quoting from those letters, right. Remarks from the field about exactly what makes it...what is necessary to make this possible, I think that would be the most persuasive evidence we could provide. And
they'll give it to us.

DR. LO: Great. But I think ... what am I trying to say here...I guess, to present a solution that we know has a lot of practical difficulties without also taking the lead and suggesting how to overcome difficulties, sort of undermines our report. I think if we just say these are the things that we recommend, yes a lot of this is more for the IRBs, yes, we know it's tough, and please address the situation. That's not going to be as powerful a report as ...and these are some of the things that we recommend that institutions and the federal government do, and this is something simple like allowing extra indirect costs for NIH grants to cover some of this would be a tremendous boon to big research institutions. And I think unless we make some recommendations that really are going to make this happen, it's going to make us look naive.

MS. CHARO: You're not suggesting, though, that we try to actually debate out to the point of consensus specific recommendations on the change of the entire standards we want them to enforce. That they are integrated and you can't separate them. And we all said intellectually that makes perfectly good sense. But as a practical matter we can't manage to figure out how to write a report that covers everything because it's a 10,000-page report that will take 15 years and we will have gone out of existence before we get there. So we were stuck with this practical problem of how to tackle jungles. And I'm wondering if we can avoid the need to try to debate out specific recommendations. If it's enough to say we've gotten evidence from the people who commented that these are the kinds of things that we're bound to wind up recommending eventually, which is better staffing, better financial support, increased representation on the membership of the IRBs, perhaps some possibilities about performance standards or certifications or licensing or some other kind of quality assurance in this system, but we have not yet gotten to that point but we promise you we will by the turn of the century.

DR. MIKE: My suggestion, Bernie, is that we can all write individual comments on these reports, so if you feel strongly about reemphasizing that point, it's something you can write. But I agree with Alta. We're recommending policy, not operational changes. I don't think we can do both in reports of this.

DR. CHILDRESS: Other points you'd like to make about the draft to guide staff as we try to again go through the several steps we need to produce another version for September?

MS. BACKLAR: I want to make sure that we understand, I want to go back to the
legally authorized representative, and I'm not certain if that's still a little confused. Where we are clear, where it is the person who's the subject who picks that, appoints, chooses a person they trust, and it seemed to me, I found places where it was slipped in...it was imposed upon them, and I'm a little concerned about that confusion.

DR. CHILDRESS: We have both. But the prior would be the individual selection and then in the absence of that the legally authorized representative according to state laws. I think we have both in the report. But there is a priority, there is a ranking.

MS. BACKLAR: Right, I want to make sure that we're very clear about when which happens because one wants the person choosing in every instance where one can have it. And as we know from Greg Sachs' research, people even in certain stages of dementia can still choose people that they trust.

DR. CHILDRESS: Jonathan, any comment?

DR. MORENO: I think it's mainly an editorial matter at this point, Trish. I really think we're pretty clear about that.

MS. BACKLAR: I have marked pages where I find it confusing and we could e-mail about that.

DR. CHILDRESS: Other points? Mr. Chair, it looks as though we're talked out on this subject. Well thank you everyone.

DR. SHAPIRO: Okay, just looking over these issues, I think we've gotten some very good suggestions today which will certainly help us improve this. I think the issue of increment over minimal risk is not going to go away, we're going to have to resolve that. We'll have to see how we can work with it but that's going to be a decision that's still in front of us. I don't see that we came to a conclusion on that today. We didn't force ourselves to vote on just what it is, but I think that's something we ought to pay very careful attention to, and each of us try to think through whether this is really a distinction worth making. And in my view it's because different, as Bernie has suggested, different protections would flow in, i.e., not have to go to the Secretary under certain circumstances or not. And it's really that question we should ask ourselves and see where we all stand on that. And let's try to exchange ideas on that over the next weeks by e-mail and so on so I don't think it's sufficient to leave it to September. We have to sort of...we'll
formulate some ideas and then we have to start working with each other on it.

D R. M E S L I N : If I could just make a request couched as a plea, if you have marked-up copies of either of the reports, please give them to any one of the staff members or put them in an envelope and send them back to us. We are engaging an editor so all of the comments of either an editorial nature or conceptual nature will be incorporated into the next draft. Where there are issues of disagreement, I would certainly propose that we use our NBAC e-mail list and that if not just a one-to-one exchange that you share it with everyone on the list, everyone can see what your views are; if you would like to join in the conversation I think that would be most productive to staff. And the sooner, obviously, the better. And we will inform you on an ongoing basis as we receive public comments, not every single one, but as we develop a small critical mass we will share any of those with you in whole or in part. Please feel free to ask, but you will be getting notification of it anyway. We'll also be letting you know about the two consultation activities, the protocol review activity that Trish and Alex and Jim have agreed to assist with. And the other activity is relating to conversations with the Maryland Attorney General's office, the New York Department of Health, and officials at NIH and NIMH as we all begin to review each of the drafts in progress to see where overlap is and gaps may exist.

So we'll keep you as up-to-date, and obviously please communicate with us as regularly as you can.

D R. S H A P I R O : Okay, other comments on this? Because if not, what I ... depending on the will of the Committee, I would suggest a short break and then we go back and see if we can pick up some of the material from the materials report, so to speak, because we hadn't gone through that whole memo and there may be other issues as well. And we have some time here this afternoon, I think we should try to get a little further. Why don't we...it's now about seven or eight minutes after three, why don't we try to be back at 3:20.

D R. S H A P I R O : Colleagues. This morning we were looking over the various recommendations/guidances etc., various statements if you wanted to get some discussion on. We got all the way on page 7 of the memo that came along with the human materials draft. We got through recommendation 6; that is, we got some comments/materials on that and we'll recast that and write along the lines that have been suggested this morning. We now have the two next recommendations, recommendations 7 and 8. Really we perhaps ought to consider together whether one is sort of a notion
again which we may want to change or shift the focus on which recommends that somebody else do something, namely some scientific community, whatever that is, to agree on a set of practices that would eliminate the need for a complex recontact efforts. And recommendation 8, either the therapeutic or the research, clinical or research contents. And recommendation 8 really deals with a similar matter but that has to do with collection of prospective collection of future samples. Now the, as I see it at least, the key issue here is whether and to what extent we want to encourage comment on, say, something in detail about the nature of the consent that would be obtained when collecting materials in ways that would make things simpler in the future. Obviously this deals with prospective samples, and so the question I want to ask is is this something we want to address and if so in what way do we want to address it? Do we think it's a good idea; in that case how do we want to opine on this?

DR. LO: Yes. I mean to pick up on the theme that we were discussing two breaks ago, I think that as with all our recommendations or guidelines, the more we can flesh it out the better.

-And for recommendation 7, I think we've already discussed a lot of elements that would need to go into a set of standard practices or best practices, I'm not sure which, and some of them I think include having a community advisory board, having set policies establishing some sort of written procedures for determining both the scientific validity of requests to use the archives and stuff, some mechanism for coding that meets certain standards. And so I think to the extent that we can at least start to point people in the direction and leave it to others to flesh it out, given that practice is evolving and people in the field who are really working on it probably can come up with better ideas in detail than we can, yet still to give some direction I think would be useful.

DR. SHAPIRO: And we do have at least a modest collection of what looked like best practices from our...we got that together and we've got those forms etc. and guidelines, various institutions which I think do a good job here or at least some of the better jobs I've seen. And we can certainly take guidance from that.

DR. LO: And then the other thing which was suggested just a couple of meetings ago was to really give NIH the sort of recommendation that they put some effort into having consensus conferences, training, model training programs, funding people to do research on how to do this better. I mean make it really come alive, put this in as part of
center grants and stuff to facilitate further developments in the field.

MS. CHARO: I think in fact we may, depending on how much time we have and how much attention people want to give it, we may be able to use some of those models that we now have and ourselves pull out the elements that seem to be most essential that we would want to make sure are included in whatever becomes a standard model. Especially keeping in mind Allen Buchanan's analysis of this situation as one in which it's not genuinely informed consent that we're obtaining because it's not really possible to consent to that which you do not know. It's really about prior notification, in which case you want to alert people as much as possible to the variety of things that may happen so that it's a no-surprises scene. And some of the elements that might be pulled out could include such things as the distinction between research that plans to come back to you with its results and research that does not plan to but might yet do it because of something surprising, versus research in which it will never go back to you under any circumstances, no matter how useful it might have been; alerting people to the complexity of state law with regard to discrimination and the fact that in a transient society no matter what your current state laws are you may not know where you'll find yourself on the day when this information might possibly be used. And looking through these forms ourselves and maybe pulling these elements out might give this guidance even more robustness.

DR. COX: I certainly agree with what's been said so far. The ... one point, though, at least in terms of the wording of this. If it could be read that saying the only reason one has these complex recontact schemes is because people are just not being clever enough to avoid them. And there are certain types of research that it's incumbent upon the research to have recontact. So that just so we're sure that the wording isn't done in a way. And there are many types where it doesn't have to be done at all. So just so we're sure that the wording is such that we cover that and have the whole system be as simple as possible because otherwise the implication is that the only reason to ever do this recontacting is because one's just not being thoughtful. And I think that my second point is this one about prior notification. I think it falls under this contact of respect for individuals, so you tell them that these are the possibilities that are about to happen and then as we keep hearing, if it's nine percent of people that say yes, you told me, don't bother me anymore, just go ahead and use it, then that's important information. But it still doesn't obviate the need for the respect of telling people ahead of time by my view. But it's pretty cheap to tell them ahead of time; you don't have to go back and send them a million-dollar questionnaire to ask if it's okay later on.
DR. SHAPIRO: Any other comments? I think with this, as with others, some of the other recommendations and so on we dealt with today does need to be fleshed out in ways that Bernie and others have suggested. And I certainly intend to do so. I just wanted to be sure this was something you thought was important for us to address. Any other comments? On this? Well, what about recommendation 9? At the bottom of page 7. Eric, do you have anything with respect to 9?

DR. MESLIN: This is an issue I think that Bernie has already alluded to with respect to additional feasibility of doing any of these things. So as a guidance it's one thing to offer the idea about the termination for need to reconsent, etc. is important, but that's...that may be more of a judgment or a guidance or educational issue rather than a particular type of recommendation. So I'd be delighted to hear Commissioners' views as to whether that responsibility can be operationalized in any particular way rather than just say we recommend that it is their responsibility. If it's self-evident, we should probably say either why it is, which I think is easy to do.

DR. COX: But I have a comment on this. If we don't make clear and crystal clear what the sort of priorities and goals are, then the investigators are not going to know whether they should come back and worry about it. And Mary Claire said that several times. Even she, as sophisticated as she is, you know, was still trying to go back and forth about really what are the principles and what are the rules. So that the...I think we should strive as much as possible not to be able to have anyone say that, that they don't understand what the rules are. Because that's a double-edged sword. Some people may not understand what the rules are, but I play basketball with my four-year old, and he doesn't understand the rules for a different reason because he wants to win. So the...and I think it's the same thing here.

DR. MIIKE: I think we have to be careful about these because they seem to be in dark opposition to 7 and 8, because 7 and 8 say let's re-obviate the need for recontact, and yet the following one says they should be monitoring when they should reconsent. So I think....

DR. COX: I think the issue, too, I think that's right, actually. I think the issue here is for us to clarify when the reconsent process gets initiated and how one thinks about that. And when that's not necessary. And 7, 8, and 9 are dealing with it in various different ways. I really think it's that issue and I think your point is well taken, that as just
written down here. That's not clear and I just think we have to put these together. One more suggestion, that is, Mary Claire's example with the tomoxofin will be an extremely powerful example to put in a report, not only the way she handled but alternative ways that one could have handled it.

M.S. Charo: In some ways I'm sorry that Alex had to leave early because he once wrote an article about informed consent that held some lessons that I think are valuable here. If we go back to Mary Claire's protocol in which people have consented to research looking for markers but now in fact we're looking for the actual gene, it was a genuine interpretive question here about whether or not the consent they had given originally was sufficient. And in the article on informed consent, Alex walked through the different points of view from which one could answer the question. Whether a professional would say that this is in fact substantially different is one way of saying has this changed enough. The second way is a more subjective view from the point of view of the patient to hear the subject and ask, would the typical subject feel that this consent had covered this new scenario or would they feel that this was new. And in the law, we've got a very confused set of rules about which point of view ought to dominate, but I do think that in a research context it would be appropriate to conclude as a principle that the point of view that ought to predominate is that of the subject. You ask would a typical subject feel that they had in fact consented to this particular kind of research and use that as your benchmark, rather than the IRB's view or that of the professional. It's different in a clinical setting, but in a research setting where essentially the subjects are doing you the favor of being volunteers, one tends to be more considerate of their subjective viewpoints.

Dr. Lo: Could I follow up on Alta's comment which I think is very, very helpful. Is the implication then that we need to have a community advisory board and somehow that board is given the choice?

M.S. Charo: IRBs are the role of trying to figure out what a typical subject or potential subject would think, feel, or say. They do it all the time when they look at consent forms and ask, "Is this comprehensible and is this sufficiently informative?" They always do that with the subjective viewpoint of the potential subject in mind. It strikes me that good IRBs frequently ask for a consult when they feel like they're out of their depth, and this is certainly another example of a case where they might want to. But mostly I think it's to remind people there that the shoes they should be wearing when they say, "Is this really any different?" are not the shoes of a researcher or a trained medical
professional. They are the shoes of somebody who is a layperson who is reacting to this, not from the point of view of technical matters but from the point of view of emotional matters. And that's often enough. Hopefully it's most of the time enough. But they do their best. The obligation is for them to do their best to figure out what the typical subject would want.

D.R. LO: Again, if I can just take a second to try and flesh this out. Would we then, having said the IRBs, the proper locus, say the IRBs ought to have someone on their panel who's an expert in this kind of genetics research and adequate representative of community or representatives of the subjects of the study?

M.S. CHARO: They already have a layperson on there by virtue of the statute.

D.R. LO: Right. But we were concerned before about whether one layperson gets drowned by the 33 other professionals working in the institution.

M.S. CHARO: A very valid concern, and yet another one for the list of things to worry about in a kind of generic look at the whole system and whether it has the capacity to carry the burdens that have been placed on it.

D.R. LO: And again, are we asking IRBs to take on yet another tough issue?

D.R. SHAPIRO: I think in the terms of that latter point, Bernie, the statistics, someone mentioned before that 10 IRBs have 48 percent of the protocols, obviously some very large workloads around. It seems to me that there are putting the resource issue aside a number of solutions to this. That is, that IRBs that are dealing with that many protocols probably have a lot, or regularly get protocols that have or are dealing with genetic issues or regularly get protocols that deal with human capacity issues in a sense. And therefore there's plenty of room to mobilize your IRBs in a somewhat more specialized way than we often do. Now that's a resource issue; I understand that part. That just leads you back to the resource issue, but it seems to me there's no lack of potential solutions if one feels this is all important enough to put some resources behind it. We have to think of how to do it and so on. And my view on this is if we think it's important enough, my test is do I want, well I suggest we spend some resources; that is, do one less NIH grant because we have to put the resources here or something of that nature, not institution by institution, but it comes out somewhere. You know, that's a test I use in determining myself. Am I willing, is this important enough that I'm willing to forego some other thing we could do with this money? I don't mean institution by institution but as a whole social policy. And if it doesn't pass that test, then it doesn't pass
the test that it's important in my view. Except for once in a while, once in a great while. Okay. There are recommendations 10 and 11. I understand 11 better than I understand 10, frankly. But let's see. Maybe Eric can help us make sense of what we're talking about in recommendation 10. There are two parts of it, and I presume this has to do with, Eric, what happens when using this material for some new project. That's the context, I presume. I can't really quite figure it out.

MS. CHARO: You know, the way I'm reading 10, it actually is not terribly consistent with what proceeded, because of course these were not meant to be consistent with one another. They are truly alternative recommendations. The way I'm reading 10 I understand it this way: Prospective consents can be used only with regard to protocols that are going to involve unidentifiable samples. In other words, you can allow your sample to be put into the great pool of unidentifiable or not. Prospective consents can't be used for future research that involves identifiable samples because we are not going to waive the usual individualized consent requirements. We're not going to let prospective consent trump it. That's how I'm reading 10. Am I understanding it accurately? Can I say that I don't like it?

DR. SHAPIRO: Yes. [LAUGHTER]

MS. CHARO: I don't like it. I think that prospective consents are not a bad way to go. It may be that we want to give some more thought to the idea of prospective consents being used not to eliminate the need for recontact, but to ameliorate it for an opt-out as opposed to an opt-in consent in the future. For example, I contract with you to agree that an opt-out is sufficient. But I think the prospective consents are tremendously useful and in the long run, can make a research endeavor far more efficient. And I hate to hamstring them from the very beginning.

DR. MESLIN: I was going to say, at the risk of trying to move you one way or the other, one of the reasons why we presented that type of recommendation, somewhere after recommendation 8, which was the recommendation that says there are a number of nice consent forms and processes out there that we might want to recommend to people, is just to juxtapose them. We heard from the NHLBI. We heard from NAPBC. We heard from a number of groups whose general and/or tiered consent activities relate precisely to what you I think would like to see. So you might just simply want to reject the concept of...
recommendation 10, but I would encourage you to think about adopting what is in recommendation 8 if you want to reject that.

M.S. CHARO: But this would be yielding to manipulation by the drafters of this memo.

D.R. MESLIN: Well that's why I waited until 10 before.

D.R. SHAPIRO: The issue of this consent is what consent is valid for future consent not completely known at the time procedures or uses of a material is not that different from what we were discussing just a few moments ago in the advance consent. It was a very similar kind of problem. And it's a generic problem and it's worth thinking about as to whether, just how narrow Bernie's example before was, that if we interpret this consent very narrowly, he has a lot of trouble. He may have trouble with it anyway, but certainly if it's interpreted very narrowly let's say MRI versus image studies it makes a big difference, probably, to how he would feel. He may not like either, but at least he'd feel differently about one versus the other. And really that's the same; it's in some sense the same issue here in different guise. Just how much can we say that advance still feels acceptable to us? So for example, in the case of Alta, or the proposition Alta just advanced, do we feel that some kind of advance consent which is general, together with an opt-out or something, is really informed consent or at least sufficiently close to informed consent that we would be happy to deal with? I think that's a very interesting issue. Larry?

D.R. MIKE: You know, I want to reintroduce a notion I talked about a while ago, which is that I don't have a problem with giving advance consent or use of my tissues and they know who I am so long as the information that they have is limited in time. I would be very offended if they never contacted me but they were delving into my medical record subsequent to the giving of the tissue. So I'd at least consider a notion of the advance consent about the timing, the time framing, which I understand what I'm consenting to. I can't consent to information that may be generated in the future about me of which I have no idea at the time that I'm giving consent. But I can certainly accept the notion that, if I went in for a cancer biopsy, anything they wanted to know about me in that episode, if they asked me and if I said yes, I would feel comfortable with it. But I would not want them to continually delve into my private life without my knowledge.

D.R. SHAPIRO: Regarding future access to your medical records. Bernie?
DR. LO: There were others before; I was just trying to get in line here.

DR. COX: I really agree with that and I really support the idea of this prospective information. It's not really a prospective consent, but it's telling people sort of what the rules of the game are again, that we don't know exactly how it's going to come out but here are the things that are likely to take place. And that's a situation where I can really go for an opt-out, because if people say, "Listen, I'm one of these people who basically I've signed up for research that I'd like to know what you're doing but if you don't hear back from me, go ahead and do it." Now if somebody's already told me that, then that's how they feel comfortable doing business and that they will get information from me so that when I know more, they know more. But it's two different ways of doing it, either getting assent from them or getting them to opt out. And not only is it respect, but it actually has merit to it from the point of view of having better understanding of the people. It gives people options, real options. But my biggest concern is exactly what Larry brought up, because this isn't a carte blanche to go into somebody's medical record whenever somebody else wants to do it. So the original research that you get involved with has to be time limited and/or content limited in terms of medical record entries, which are often enough I believe.

DR. LO: I want to try and see if I can draw together some of the comments which I agree with and I think are very helpful. I like option 8 rather than option 10. And then looking at option 8, I would like us to encourage tiered consent and to discourage general consent because I think that's so vague as to not really be consent at all.

And I just want to raise a couple points for discussion or clarification. One, tiered consent plus an opt-out sounds good, but we need to keep in mind that using the opt-out too often can be an invasion of privacy if every time they want to do a new study I get another postcard. I'm moving around the country trying to escape from my past and they keep tracking me down, I may not like that. And then I want to pick up on Larry's point. I think it's really important and I think there is a big difference, as he pointed out. But I want to test what the boundaries of that are. So on the one hand you use the sample but not only use the clinical information existing at the time of the sample, but 10 years later using publicly available information from death certificates, look at overall mortality and whether a given gene predicts that. So presumably that would be okay if it's publicly available information. Okay. How about going to a little harder case, cancer registries, and saying that I've given consent in 1998 and in 2000-whatever, 10 years from now,
2008, the investigator says, "Well, I'll go to the local Northern California cancer registry, which has all the cancers of interest in their registry, not going rifling through my entire medical record, but finding out something about me. Does that fall under your invasion? Would you be offended by that?

DR. MIKE: If I'm dead, I wouldn't care.

DR. LO: But you wouldn't want a researcher to look in a cancer registry for a 10-year prediction of the...

DR. MIKE: That's a hard case. But if they're trying to find me in this registry, then to me they're delving into my personal life, subsequent to the time I gave permission.

MALE VOICE: So you would have wanted them to have said up front, "We're planning...

DR. MIKE: But obviously there's another issue sitting over here. Do cancer registries, is that my personal information? I don't know.

DR. LO: Well, it's linked to you. It would have to be linked to you.

MS. CHARO: Mary Claire King's research, in which she talked about how ideally she would like to have had survival data, is exactly the kind of research that might require repeated trips to your abstracted medical records over a period of two decades. And she was doing that research with a single opt-out moment, in which people opted out at the very beginning but were not subsequently recontacted to say, "Well, it's been 5 years and every 5 years we always go and check and see if you're still alive. Do you mind if we go and check and see if you're still alive?" Do I understand you correctly saying that you would like her to have had...

DR. MIKE: How is she gaining access to my medical records?

MS. CHARO: The medical records are being abstracted by somebody who's on somebody's payroll to do just this. They're told which medical records to pull.

DR. MIKE: I know. But how are they pulling my medical records? How are they getting access?

MS. CHARO: Because you were initially in the study because you did not opt out.
DR. MIIKE: Yes. I understand that. But how are they getting my clinical records?

MS. CHARO: In the first place? How are they getting them? Well, you know, that's a practical problem that varies from research protocol to research protocol. If there is a registry, probably this information is being sent to the registry on a regular basis by all of your various attending physicians because they are all part of the process of collaborating with the registry and you've been collaborating actively because somewhere along the way you said it's okay for you to continue to collect data while you treat me and send abstracted versions to the registry.

DR. MIIKE: Well, that's a different situation where I was actually told that and I said yes. So I would feel comfortable with that. But I would have had the opportunity to say it's okay. It's just the situation where they're accessing information subsequent to my saying yes.

MS. CHARO: Like, for example, recontacting your attending, assuming that you're one of the rare people who has the same doctor for two decades.

DR. MIIKE: Yes. I wouldn't want my doctor to be providing information without their ever telling me that my personal doctor is providing information.

DR. COX: This is a recurring thing that happens right now. When researchers hook up with Kaiser or other situations and Kaiser says, "Sure. We've got a contract with you. You can look at our patients." When the researcher calls up and says, "You know, your doctor said it's okay to call you," not very many patients object, but it only takes one to shut the study down. And that patient then says, "What the hell's my doctor giving you my records for?" On the other hand, if you do this and you say, "I'm calling from Kaiser. I work for Kaiser and we're asking, is it okay to use your records in this study," And people say "Yes. It's fine." And then you go and you ask them questions. So you say, well that's a trivial point. But it's the difference between being able to conduct the research and not, because it just takes one person; that's all it takes. And these aren't theoretical things. These are real things that happen every day right now. And it shuts down $\chi$ just 2 days ago I had an example of this in Hawaii. It shut down the study for 6 months.

DR. MIIKE: I wasn't the patient.

MS. BACKLAR: We wouldn't do it any differently in a research protocol with mentally ill people where I'm getting names from the information system and then I have to get somebody from the state to contact them first to see if I can contact them. So it's
exactly the same situation.

M. S. CHARO: It's a very commonly misunderstood. People think that review of medical records in order to determine who should be recruited is not subject to these requirements. They're wrong, but this is a frequent misunderstanding I've discovered. But, Larry, your situation's not about recruitment. Yours is somewhat different. I mean, basically, if I understand you correctly, you are advocating that a single moment of giving permission to be a research subject in some fashion, a single moment in time, is insufficient if being a research subject is going to involve multiple requests to your physician to go into your records and abstract them for the researcher.

D. R. MIIKE: Let me put it at a gut level. I can distinguish my personal self apart from a piece of my tissue that was taken from me a long time ago. If they continue to look into my medical record on my living self, that's a little different from giving permission. But it's that level that I'm talking about.

D. R. COX: Larry, can we ask you a question? What if somebody said, "Listen, what we want to do is we want to look over 20 years for this piece of information."

D. R. MIIKE: Well, that's different. Then they've asked me that specific question.

D. R. COX: I don't think it's actually the multiple times going in; it's up-front telling somebody what you have in mind of doing. So that's exactly what happens with a lot of these things. You get tapes. They become public tapes of these longitudinal studies, but it's clear what's going to go into those tapes up front. And you don't come back halfway through and say, "Oh, by the way, now I want to actually start looking at an additional X, Y, and Z." I think that's what you're objecting to, Larry, and that's what most people object to. But if up front you could basically say what you're going to be assaying or sampling from the chart, then I think most people . . .

M. S. CHARO: Right. But they could have told me when I gave permission like this that we're going to spend the next 15 years going into your chart once a year, looking at your mammogram results, right? And they're doing that, and then along the way somebody suggests an association between breast cancer and abortions, or miscarriages, or years on the birth control pill. And so now, 7 years into this, what they're going to do is they're going to go in and they're going to pull that information. And that is distinctly different, and yet it's part of the same study when they suddenly are thinking, "You know,
we might be finding an association here."

DR. COX: But that's not kosher because basically what you're doing is that you're doing something different in terms of the body of information than you set to begin with.

MS. CHARO: Right. But these prospective consents are written very generally. And the point is do we want to permit these to be written generally enough that people can say, "Yes. You can go in and you can use whatever you want over the long term." Or are we going to prohibit people from doing that because we think it's so far away from . . .

DR. SHAPIRO: The big difference here, whether we're dealing with identifiable or nonidentifiable cases, nonidentifiable are not a hard, nothing very hard for me. We don't have to spend any time right now. It seems that we're dealing with the identifiable cases. And my own view is there are limits to this prospective consent, and they're pretty stringent. And that is that you can't just X1 mean I can't quite imagine there's a certain amount of tiered consent you can do at various times I'm sure X and well look at what some of the people attempt to do X but there are limits there because if you're going to have the kind of permission that lets you go back into the medical record, that's a serious matter, a very serious matter. Go back without reconsenting. Let's see here X Bernie? Bette? Bernie's had some chances. Let's start with Bette.

MS. KRAMER: I'm confused. I had thought that the proposal was a prospective consent for continuing use of the sample, but that that did not include consent to continue to access the medical record.

DR. SHAPIRO: I think that's an open issue. That's a question of how we want to, how that original consent is structured. It could be structured either way in principle.

DR. COX: And that's what we're saying, Bette, but then there's a coda on that that if you tell people up front that you're going to access the record and for what, then it's a bounded thing in the beginning, and people get a chance to consent to it or not consent.

MS. KRAMER: Yes. But they're two very different cases. And I think we need to distinguish them.

DR. MIKE: You know, Bette, I would say, "Yes" if they said, "We want to follow your case and the medical record for this specific issue." But if they say, "We want access
to your medical record indefinitely to do research," I'd say no. I'd say you have to come back and tell me for what reason.

M.S. KRAMER: That's the third distinguishing . . .

D.R. SHAPIRO: Right. That's not consent in any way. It wouldn't qualify in my view. Bernie?

D.R. LO: Realistically, I think what we're going to do is reinforce the tendency to develop large cohorts specifically for the purpose of doing research, so this is a take-off on Framingham \( \chi \) Heart-Lung, which is doing this. There are other large prospective studies because, in point of fact, the information I really want to get is not in your medical record. I want to come back and ask you questions about various genetic conditions, family history that probably I can't get at through the computer. And realistically, I think what we're going to be seeing is these ongoing studies where you agree to be contacted on a yearly basis and they ask you, "Is it okay to ask you these additional questions?" or to do this or that. Sort of the prospective, ongoing nature of the followup is built in. I think ethically, that's much more acceptable because there's that ongoing interaction that means you're not doing things that people didn't understand and didn't consent to. And frankly I think for the researchers, it's a better design because you get the chance to ask the questions you want to ask rather than having to hope that it's in the chart that was there for other purposes but that's more expensive. And you've got to realize that. To put together these cohorts costs money.

M.S. KRAMER: But that's like I said before. We do longitudinal studies like that where you go back every 8 months, every year to follow a subject over time. It's part of your research plan.

D.R. SHAPIRO: Okay. There have been some helpful comments, but let's move on here to look at recommendation 11 here. Eric, do you have any comment on that?

D.R. MESLIN: I think this is a bit more straightforward than 10. We're really speaking about prospective collection and the requirement to obtain an informed consent in order to use that sample. I may just say in passing that, having heard the conversation about essentially recommendations 7, 8, 9 and 10, one way of getting to Bernie's helpful question about tiered consents, is that we could summarize these
concepts in one or two recommendationsXone relating to what we are expecting in the prospective consent process, both in terms of the forms that may be developed and how specific we would expect those forms to still qualify as consent documents and how general they would be to still permit use of those samples without an opt-out. The Commissioners have mentioned that there are examples where individuals have indicated that they would be prepared to have their samples used, but the more uncertain you are about what is going to be done with them, the less that should count as prospective consent. And we haven't set that boundary.

Recommendation 11, which could have occurred earlier in the list because it's supposed to be a bit more straightforward, is simply meant to indicate that this is the best-case scenario, the prospective collection of information from a sample, use of a sample whether stored or collected, where the information can be linked back to the individual requires what we're calling full informed consent, and that's the informed consent we're all familiar with, a listing of risks and benefits and the like from the regulations.

MS. CHARO: I do have some difficulty with some of the language that's being used in this to express its ideas. I find myself uncomfortable with the parallelism between a sample that's linked to an individual being made parallel; that is, his identity is not concealed from the researcher. The identity probably is concealed from the researcher. It's probably coded. And so I think that that particular sentence actually offers the possibility of a fresh round of confusion. I'm also uncomfortable with the phrase "full informed consent." I found myself scribbling, "as opposed to partial." Now I can, however, understand that informed consent as opposed to a mere opt-out might be what you have in mind but would like to again suggest that these phrases might be confusing.

DR. MESLIN: Well, your point, Alta, is that it's largely editorial. It's not that there's a conceptual confusion. The language is saying "full," which I believe we understood to be....

MS. CHARO: Well to be honest, I wasn't sure what this meant until you just explained it because the language was so confusing to me I really wasn't sure what the agenda was behind that particular recommendation. I read it four times and then just left it in red.

DR. SHAPIRO: Are there any other comments beside with respect to what is marked here "Recommendation 11"? The other ones that are left here are reallyXI don't
know if they require any discussion right now. We'll have to wait. They're really just . . .

DR. LO: Before we move on, recommendation 11 seems to restate what's the current situation, that if it's identifiable, right, not linked, you need informed consent. Conversely, I guess, do we want someplace to affirm that, if you have a sample that's already been collected in the past and you're going to be using it . . . I guess I'm asking a question. For all these stored pathology samples that are currently in hospital pathology departments that now are linked to somebody's medical record number, are we going to allow those samples to be used if they're given to the researcher in an unlinked fashion? If the pathologist just says, "I'm going to close my eyes and take 150 samples of Cancer X and I'm not going to know whose they are and send them off," we're going to allow that. Bette says no pathologist would ever do that because they're such compulsive recordkeepers. But if they were, are we going to . . . The question keeps coming to me. We heard a lot earlier about this is a valuable resource, there's a lot of good research that is done on that, we shouldn't sort of throw that away. I want to try and be as clear as we can about what are we going to allow to be done with those archived samples?

MS. CHARO: If they're given without identifiers or if, as Mary Claire King did, the links in those codes are severed irrevocably, it's my understanding that we were comfortable with the current rule which says they can be used with impunity.

DR. LO: Okay. So you were saying it's not how they're stored in the archive, it's how they're given to the investigator.

MS. CHARO: It's whether or not the individual is identifiable. It's neither how they're stored nor how they're given. It's whether, in the end, the individual is identifiable. That's the real question, is whether or not the donor of the tissue could ever be identified. And a severing of the link is one way to make that individual unidentifiable.

DR. LO: Okay. For Bette's pathologist, to make this work, the pathologist at some point has to delete the code.

MS. CHARO: That's right. That's another way of making them unidentifiable. By the way, since Bernie made us go back to 11, let me just say that it's actually written a
little over-broadly the way it is, because it does not include the exemptions and exceptions that currently exist. Not the exemptions, sorry, the exceptions that currently exist that permit a waiver of consent.

D.R. SHAPIRO: Any other comments on this? With respect to the remaining ones, I'm . . . It doesn't seem to me that we need any real discussion right now. These are kind of XI hate to use this word but they're little sort-of "mop-up" suggestions here, which we will get to, but there's more important issues to deal with. It's not that they're unimportant. So I'm just open for any observations, suggestions you might give.

M.S. KRAMER: Harold, a question. Back up a minute to the last issue. Wasn't that one of the cases that Dr. Hook talked about at the last meeting, where the cohort that was givenXI'm trying to remember now where the cohort that was given was small enough . . . I guess it would depend on whether or not the repository or the pathologist in question was willing to destroy any record of the samples that they were given. Do we know practically whether or not that would happen? Alta, is there any legal liability on the part of a repository to keep a record?

M.S. CHARO: Well, I don't know the answer to that. But I can tell you as a lawyer that if they hadn't kept a record and there was a reason why it would have been helpful and it turned out somebody was harmed, I'd make a good argument that they should have kept it.

M.S. KRAMER: Yes. I'm just thinking about that. I wonder if any pathologist or repository, in fact, is going to destroy a record of whose samples.

M.S. CHARO: I think more realistically what will happen is what Mary Claire King described. The repository has the samples listed under a set of codes. There is Code A, B, C, D, and E. And they will take those and they will give them a new code, 1 through 26, and they keep a little record that says, "A equals 1, B equals 2," and they give 26 samples to the researcher that are labeled 1 through 26 and the researcher uses them. Would this repository ever destroy the record that says, "We gave away samples A through Z"? Probably not. Might they destroy the record that says, "A equals 1, B equals 2"? Yes. That's what she did. And by doing that, they know as a group what was given out but they cannot do a one-to-one correspondence between a specific sample and the results the researcher found and the particular donor of that sample. That they would do, and they'll do with some hesitation because of the possibility there would be some day some valuable reason to link back to the donor. But they will do it.
DR. SHAPIRO: And if they don't, it just means another set of protections gets initiated. It doesn't mean you don't go ahead. It doesn't mean anything of that kind. It just means another set of protections comes in. They're now identifiable and you go down that road, that's all.

DR. COX: But you see, one of the things that we haven't stated here yet that certainly isn't in the common lexicon of most people is the possibility that things are identifiable. But, it's that when it goes to the IRB, you have approaches in place that say that that information won't go to the researcher. And what that does is lower risk than if you don't have those things in place and you consider it differently. So I think, just because it's identifiable, the research community does now, it's identifiable. Then everyone has that stroke. So it could be under different...

DR. SHAPIRO: Yet another harm.

DR. COX: Yes. Exactly. Stroking our researchers. But I think that... So then they go to these extraordinary efforts to destroy all the links. Well, I don't think we necessarily have to do that.

MS. EISMAN: I'd like to address that point that Bette asked because it was a point that Tom Murray asked me to address after the last meeting. And I did do a bit of research, not comprehensive research, but did talk to a few repositories about their practices for dealing with unlinked and coded samples. And I think David Cox yesterday made the very good point that it does appear that the vast majority of samples are used in a coded manner, not in an unlinked manner. And that is actually more rare than I even expected it to be. A lot of repositories don't destroy that link and they know who the samples come from, but they do also have a... some of them also do have a statute that, when they send out samples to researchers, the researcher can't come back and get any more information.

-So even though the repository knows that Sample A is John Smith, when they send it out to the researcher, the researcher can't come back and get any more information than was originally sent. So whether that's considered coded or linked is one question. The other question is about unlinked samples that in most cases there is a list kept of who those samples came from. So if it's 50 people, there is a list of those 50 people that the sample came from for a number of reasons. The main one that was cited was quality control. They need to know who those samples came from because, if the researcher came back and said, "I need 50 additional samples completely different than what you first sent me,"
if they don't know who they came from, then that repository can't function. So those are
a few points I wanted to make.

M.S. KRAMER: Then what does that do with the definition that we accepted, that
if, no matter how far-fetched it is, if there's anybody who can link, anybody who can
identify who the samples came from, then we're calling that identifiable?

M.S. CHARO: It is. Because it can be done and a circumstance will arise where
somebody wants to take advantage of that. You do the breast cancer studies in one of
these settings where you've maintained the links but everybody understands we're never
going to let the information go back to the donors and we don't care who they are. And
suddenly you discover that people that have the breast cancer gene seem to be at high risk
of ovarian cancer, or the next thing it's going to be is that they're at high risk of
developing a third eye, whatever it's going to be that seems to be linked. And suddenly
somebody says, "You know, it's absolutely imperative that we send this information back
up to the donors because if they get it now, they might be able to get some kind of
preventive strategy going." That is why you have to understand that these are identifiable,
because as soon as that temptation arises, you're going to have a discussion about whether
or not the information is sufficient, is the cure worse than the disease, is the information
too ambiguous? That's why you have to understand it being identifiable.

D.R. COX: But, Bette, let's go one step further from what you're saying. What are
the implications of it? This comes in my view what Harold was saying earlier about needs
to go before an IRB. By basically saying these are identifiable, it says that they go before
an IRB.

That doesn't say what kind of hoops people have to go through, so that they go before the
IRB but the IRB says, "You say you're not going to ever give information back to the
researcher? Sign in blood. Sign right here." And then when the researcher comes back
and says, "Well, but I really have to go back," you say, "You see your blood right here. You
can't do it."

D.R. LO: I understand the rationale for keeping a list of who the 50 samples were
so you can send them a fresh batch. What's the rationale for keeping the code that A
equals John Smith if David Cox has made people sign in blood they're never going to
backtrack? Why have it? What's the rationale for keeping that?

M.S. EISMAN: That's a good question, and I didn't get that in the answer when I
talked to the people at the repository. The answer was that that's how they do it. I'd be
happy...

MS. CHARO: It is so that people can go back or so that they can do subsets. For example, you sent me 50 and I looked at them and there were 10 there that have a characteristic that's interesting to me and I want you to send me 10 more of the same. Well, they've got to know which those 10 are. You know them as numbers 17, 29, 33, etc., and they've got to know which those are so that they can go back to the blocks and figure out where they've got to get another section.

DR. LO: Right. But then that violates the signature in blood they gave David Cox because the agreement was I was never going to go back about the subjects.

MS. CHARO: And indeed, David, you and I are talking about different kinds of risks. You're talking about the risk of invading the medical record or the tissue for more information. I'm talking about the risk, quite the converse, of sending information back down to the donor, which are two very distinct kinds of risks.

DR. COX: In both cases you're going back. Bernie's absolutely right that they're different risks. And that's what we need to do, is talk about what these different risks are in different scenarios. Not to try to make them go away by taking something that's identifiable and pretending it's not.

MS. CHARO: This is where, to coin the horrible phrase, how it's used by the researcher begins to get valuable, get very important, because what I want them to sign in blood is that I have absolutely no intention of sending information back down the line to the donor. Now we all know that situations can arise that cannot be foreseen now. By definition, unforeseeable things can't be foreseen. So, hey, there might come a circumstance. But I have no current intention of going back down the line. And so long as that link is maintained, that possibility is preserved. Now if you put into place some kind of system on which we have a filter so that when the investigator says, "I think I've found something that requires me to go back down the line and tell the donor," there's another body of people who say, "Well let's talk about this all together." Whether it's the laboratory's own group or it's the IRB or it's some neutral body, that acts as a check on that particular kind of risk being realized, and is exactly what may allow something to be a minimal-risk procedure even if it involves looking at stuff that is potentially stigmatizing or embarrassing, because you've put in place a series of protections against that information ever getting out.
DR. SHAPIRO: I think it's really quite important to keep on reminding ourselves that, just because it's identifiable, doesn't mean a ton of bricks comes down on the study. That's not what it means. It just means now there are other things to think about and you have to start thinking about them. They may be very small, in which case they'll be dealt with in a very simple way. They may be very difficult, in which case you will have to go through them.

DR. COX: But when you have the research community being involved with thinking about these things, that's going to be very useful because no one has more at stake than they do, at least from the point of view of carrying on business. Patients have a lot at stake. But what you'd like is for the research community to have something at stake here, too.

DR. SHAPIRO: Any other comments? Are there any comments, since we are going to adjourn in a few minutes, are there any... DR. MIIKE: Yes. What does recommendation 11 mean? Do they have to get informed consent or not?

MS. CHARO: Unless they meet the conditions for a waiver.

DR. MIIKE: But for that example, where a repository is the only one that has the code, that the researcher doesn’t, we're calling that identifiable and we still have informed consent?

MS. CHARO: Unless they meet the conditions for a waiver.

DR. LO: So if it's not greater than minimal risk and it won't adversely affect the welfare of the subject, you don't have to get consent.

MS. CHARO: And it's not practical to get consent.

DR. MIIKE: Okay.

DR. SHAPIRO: Then we agree that this is one or something or at least further up the ladder. Okay. Before we adjourn, is there anything you'd like to say now? We will have to come back to 12, 13, and 14. They have their own importance. I don't want to minimize them, but I don't know if we can productively say much about them today. Let's see what comments there are so it would be helpful. Bernie?

DR. LO: Yes. I'd just like to say this was really a very productive meeting. I want to thank you, Harold and Jim, for sort of leading us through this. And to Eric and the
staff for really sort of allowing this to happen. I think we've made a lot of good progress, had a really good discussion. I think we're getting closer to our final product.

DR. SHAPIRO: Any other comments? Well, thank you very much. It's been a long day. We almost began at 7:30; it was actually quarter to eight. It's now 4:30 almost, 4:25. So thank you all very much and let me extend my thanks also to staff for mobilizing this meeting and, Trish, thank you for encouraging us to meet here. It's very nice to be out here in Portland. We're adjourned.