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DAY ONE: Wednesday, September 16, 1998

WELCOME AND OVERVIEW OF AGENDA

DR. SHAPIRO: Colleagues, I'd like to call the meeting to order. First of all, welcome. I hope the members of the Commission had a good and productive summer. As you can see from the materials in the book, we've been busy trying to generate reports and analyses for your review and discussion. We could look briefly at our agenda before I turn it over to Eric—I think it's pretty clear that all of this morning we'll be dealing with the human biological materials report. Tom will be joining us shortly; in the meantime, Eric and Kathi will lead us through the draft that we have, or at least focus us on some of the issues that we have to discuss and decisions that we have to make. And then we'll turn this afternoon to the comprehensive human subjects projects, and then tomorrow—virtually the entire day—to deal with our report on human subjects.

That, of course, is in its most complete form of the reports that we have and we'll very interested in hearing the discussion on that tomorrow. I want to apologize in advance to Commission members that I'll have to leave early tomorrow afternoon, but Jim will be here to be sure that we get through that report on time. If there are any special scheduling difficulties members of the Commission have, just let us know during the break and we can...just make sure that we know about them. And, again, any comments that you might have so we can make them part of our ongoing discussion. So let me now just turn to Eric for the Executive Director's report. Eric.

EXECUTIVE DIRECTOR'S REPORT

DR. MESLIN: Thanks very much. I'll be very brief—I'm trying to make sure that the microphones are on and the folks in the audience hear us. Thanks, I'll use Dr. Ellis as the test subject. I only have a very few brief remarks. One is to ensure that those who are here obtain copies of some additional handouts that we have provided. There are a number of materials that came in after we were able to put our two reports on the web site and circulate them to Commissioners. Those materials are on the table for Commissioners and are available for the public members of the audience who are here. Those items include, but are not limited to, the following. The first is a comprehensive analysis of the public comments that we received for our report on persons with mental disorders that affect decisionmaking capacity. There's a memo and 16 pages of the text, much of which Commissioners have already seen but the bulk of those comments that arise have now been analyzed. We will obviously be able to refer to those comments for our discussion tomorrow. In addition, there is a very important supplemental memo for Commissioners and others regarding the report, the capacity report. This is a memo that

Dr. Shapiro, Dr. Childress, and I have put together over the last few days. A memo that draws to Commissioners' attention some unfortunate omissions in the text of the capacity report, which we wanted the Commissioners to have in their hands. You may want to refer to it over the course of today and this evening so that you are up to date in our discussion tomorrow. And thirdly, there is a paper from Professor Gunsalus, an earlier version of which had been sent to Commissioners. We wanted to not burden your briefing books with those additional papers. Professor Gunsalus will be here this afternoon to discuss her commissioned paper, and it is available for Commissioners now as well as the public. We do not expect every one to be able to read it thoroughly between now and the time she arrives. Apologies for coming when it did but Commissioners have seen the earlier draft and you will have an opportunity to discuss this with Professor Gunsalus this afternoon during that portion of our agenda. The last item that I would like to raise concerns meetings. The public in attendance here knows that we have had a regular schedule of meetings on a bimonthly basis. The Commission has decided to add an additional meeting next month on October the 20th. It will be held here in the Washington D.C. area. We will have the particulars of the location, etc. for the public as well as the Commissioners later on today. The express purpose of that meeting on the 20th of October will, we hope, be to finalize the report on research involving persons with mental disorders that may affect decisionmaking capacity and we hope that it will be an opportunity to begin an important discussion with Federal agency representatives that have been involved in our previous survey. If that meeting schedule is successful, we have also determined that it would be possible, if the Commission felt it necessary, to meet via teleconference in December, if necessary, should the Commission feel that they are in the same position to finalize the report on research use of human biological materials. So I'm simply indicating that staff has investigated the availability of the use of a teleconference mechanism which would be that not all of our Commissioners would physically have to be in the room. The public would be invited to the room where the Commission meeting would take place and we would ensure, hopefully, the highest quality telecommunications teleconference ability. We do not have a date. We have not established that as a meeting. I'm simply indicating it for the public record that that is a possibility should the Commission decide that it would wish to meet in December to finalize that report. That's all I have for the moment. Mr. Chairman.

DISCUSSION OF STAFF DRAFT: THE USE OF HUMAN BIOLOGICAL MATERIALS IN RESEARCH

DR. SHAPIRO: Any questions for Eric on any of the issues he has raised? Okay, why don't we proceed with the consideration of the draft material that we have before us. Commissioners have received a number of materials over the past two months since our Portland meeting including a revised Chapter 5, which includes summary recommendations of others. Many Commissioners have offered comments and input, and

what you now have before you is a complete revision of the staff draft, and we will be discussing it this morning. Dr. Hanna and the research staff have done, I think, a very admirable job of bringing this draft forward and I'd like to turn it over to Kathi to lead our discussion and then when Tom Murray joins us, he's coming in on an early flight this morning, he can join in as well.

DR. HANNA: Thank you, Eric. You can see from Chapter 5 that it has grown in length and I hope that it's beginning to reflect the discussions in Commission. I'm sorry it was not at the Portland meeting but I listened very carefully to the transcripts, and I think a lot of progress was made there, and I hope it's reflected.

DR. MESLIN: Can you check to see if the microphones are working? We are not having any feedback here. Thank you.

DR. HANNA: I think probably the best way to proceed would first be for me to tell you where I think in Chapter 5 we need to focus discussions and help us to fill out the report. But, then, I would propose that we just have some general discussion at first to get a sense of the Commission on where the conclusions and recommendations are going and then move into a more detailed discussion of Chapter 5, recommendation by recommendation. You can see that there are probably some new ideas that have been introduced into Chapter 5, so obviously we're interested in what you think about that, but in particular, I hope that we can refine more today the discussion about what constitutes "minimal risk" on research using human biological materials. Staff, I think, spent a great deal of time trying to work through this and trying to distinguish how research using human biological materials differs from other kinds of research, and how the research context in the usual consideration minimal risk, which often has to do with physical harms, has to be rethought in the context of use of stored materials where there is no immediate risk of physical harm. We also, in some of the e-mail exchanges back and forth between staff and Commissioners, have tried to figure out how to develop this concept of "special scrutiny" categories and what that means in terms of the IRB and how we might define protocols that deserve special scrutiny and by what criteria. The other thing is practicability, one of the conditions for consideration of waiver of informed consent has to do whether it's in fact practical—to go back and do that. I think we've tried to make a start on addressing what criteria we might use in making a decision about whether it's practical to go back and get consent. And along those lines, I think the Commission also has to think about what criteria it might use to guide IRBs when reconsidering the re-contact and under what conditions human subjects should and can be re-contacted for various reasons. Whether to get their consent, to inform them of the nature of the research that is going on or whether you're giving them the option to opt out of research. So these are very broad issues that I think are at the crux of getting these conclusions finished and I hope that today we can get a little bit further along in there. I would like to just get some general comments first, if that's okay, and then we can proceed with a more detailed discussion. I'd like to go through the chapter

sequentially if people can abide by those rules only because it was a challenge for staff to lay this chapter out in the way that it's been laid out and trying to lay out the logic in a way that you can actually start and go to the end and understand the reasoning behind the recommendations. As you can imagine, the argumentation can get very circular here and so it would be helpful if we would just start at page 1 of Chapter 5 and progress through to the end.

DR. SHAPIRO: Page 1 is 176 for those who are flipping, page 1 of Chapter 5, page 176. All right, let's check to see if there are any comments of this initial parts of Chapter 5. Do you want to go recommendation by recommendation? Is that your idea, Kathi?

DR. HANNA: Well, some of them, we could go page by page and you'll see that in some cases it reads more like a conclusion than a recommendation. One thing that Eric and I have talked about is eventually we will have to have some kind of consistent style across NBAC reports about how recommendations will be phrased and written, but that's something we can work out later. You'll see that the way that we phrased the recommendations and presented them in this report are stylistically different than they are in the capacity report. That's something that we can resolve, but right now any place that you see bolded, italicized text is where we are presenting what we think is a conclusion or a recommendation of the Commission. There are some other places where you're going to find italicized text in brackets. That's really just to signal to you that this is where we think we need further discussion.

DR. SHAPIRO: Thank you. The first of the items in bold print or italicized is a subject we've discussed before, but I don't want to just rush past it. It occurs on page 178, which talks of the adequacy of the Common Rule for research using human biological materials. That's a critical statement because it frames everything else—the context in which we would deal with other issues here, clarifying issues and other issues that need attention. So we should pause here and see if there are any questions/concerns on this issue. That's on page 178. We'll take silence to be on this issue that we have discussed it before, of course we have at other meetings, to be the way the Commission wants to proceed. Okay. Thank you. Alex, I'm sorry.

Professor Capron: In part of the lead-up to that, on page 177, at the end of the first whole paragraph—I don't understand what's intended there. Let me just read it. It says, "The Commission recognizes that the extent to which the Common Rule is adequate is determined through one's evaluation of the seriousness of the decisions that currently must be made by the investigator, the IRB, administrator, or full IRB and in some cases, a human biological materials repository." I don't know what that sentence means. Again, I can understand that the bulk of the sentence is the phrase, "is determined through one's evaluation of a series of decisions," but it doesn't tell me anything. At other places where things are unclear but I understand them, I'm simply tempted to get

used to some new language. But it would be a lot clearer if there were a reference to at least an example or something. Can you respond, Kathi?

DR. HANNA: Yes, I think you made a good point, Alex. I think if we would add some context there that there are a series of decisions, questions that have to be answered as one progresses through the language of the regulation, and we probably should introduce what those questions are right there.

Professor Capron: Since the whole point of this...two things. The whole exercise here is mostly an exercise in refinement and this first conclusion, which comes on the next page said, basically things are adequate. One is that NBAC seems to be, well, mostly that's okay. I can't tell if this is really a sentence which ought to say that it's one thing to talk about the adequacy of the regulations; it's another thing to talk about the regulations in practice, where the actual decisions that investigators, IRBs, and administrators make becomes crucial. And if that's the point, you ought to just flat-out say that.

DR. SHAPIRO: Thank you. Other comments, questions around this recommendation or the material leading up to it? Okay. Thank you very much. The next item, and in some of these cases there is a lot of material between these items. I don't mean to either overlook or gloss over it. We'll just go with the next item and then feel free to raise issues that occur in the interim. Carol.

DR. GREIDER: I had two comments. One regarding the language on page 179 under the title "Activities that Constitute Research." The sentence, line 11, that begins, "The current regulations and NBAC's recommendations do not apply to purely clinical interventions even if they are experimental in nature." I had to read this a number of times to really understand what it referred to and I thought that it might be construed to mean samples collected in the clinical context as opposed to clinical use of the samples. And that is something that we discussed many times and if we just clarify, I think that, I do understand part of the intent there. If you could just clarify that language so that others could as well. And then the other comment is on page 180, line 14, regarding the issue of criteria for exemption. And in criterion number 1, samples are existing and publicly available. Now I understand that there is a footnote that describes what "publicly available" is but I still feel somewhat uncomfortable that it's not really clear, if we really recommend this as being an exemption, that we be very clear what "publicly available" means. What publicly available means to me as a researcher—many things are publicly available that I would not feel comfortable with them being completely exempt because it was easy for me to obtain them.

DR. DUMAS: I had the same problem. And I noticed on the next page, line 4, there is an attempt to clarify the meaning of publicly available but it still does not, it doesn't satisfy me. I could say that I have a sample that was on the shelf, put on the shelf

unbeknownst to me and now it's going to be used with research unbeknownst to me, without my permission. Is that what we mean to imply by that?

DR. HANNA: We sent a specific question to OPRR to ask them to provide us with some clarification on that and to tell us whether they had issued any guidance in the past to define what "publicly available" meant. And you see that in footnote number 3 there. I agree that it remains confusing, and the Commission can take the tack that it wants to on its own terms clarify what that should mean. I think that perhaps that OPRR might welcome that kind of interpretation. And we are also trying, Elisa Eiseman is also trying to get a sense from the material that appears in Chapter 2 about how many of those repositories would consider themselves to be publicly available. Our sense is that there are not too many that would meet that criteria of being publicly available and therefore that's why most considerations then fall into category 2 here instead of 1.

DR. GREIDER: But let's say some of them do consider themselves publicly available. I would think that all of the issues that we discussed regarding the protections for those samples should equally apply. I don't see why you should say to them "outside the realm of protections" because something is publicly available. It just—

DR. SHAPIRO: Alta.

MS. CHARO: I could be wrong about this, but I think that the intent under the language, even if it's not being conveyed clearly, has been "facilitate research that uses things that are already in the public domain, and it probably was not written with human biological materials in mind. It's probably written with a great deal of other inanimate objects or information sources, such as publicly available lists of names and phone numbers, as found in the phone book, and that one might do a survey of, you know, the ethnic distribution of names and the names with vowels on the end of them. So the question I would have is if you were to think of it in that context, which it was probably developed for, what would you want in this definition and then the next question would be, is that a good working policy as far as we're concerned about human biological materials?

DR. GREIDER: One of the main points is that it says on line 14 there, "the samples are publicly available." And what we're all concerned about is the information that has already been extracted. If you have something and the information that you are going to take out of it is already publicly available, I understand why then there wouldn't be the same level of protections for it. But because, from the samples, additional information can be obtained when you have a sample in hand and that information is not necessarily publicly available. It's the information content that is important here and the word, it says the samples are publicly available. Joe Smith might have his name in the phone book and that's publicly available but all the information about the sample might not be publicly available.

DR. SHAPIRO: Rhetaugh.

DR. DUMAS: I wonder under whether or not there are conditions that are defined to determine when a repository is justified in labeling a sample publicly available. How does the repository get to that point? Does anybody know? And is that a concern for this group?

DR. HANNA: I think that it is a concern of this group. Whether anybody knows is a good question. I don't know. Elise, do you know? We can try and find out for the repositories that consider themselves to have collections that are publicly available. We will find out what conditions have to be met for it to be labeled that way.

DR. SHAPIRO: Steve.

MR. HOLTZMAN: A couple of points. I'm not sure I agree with Alta's interpretation of the historical background because we're in specifically the subsection that says "research involving" and it says "pathological specimens." So clearly they were thinking—we're in 101-b4—"research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens," so I think there was in mind biological materials. Second off, there are clear examples of repositories which are publicly available in the relevant sense. Take Coryell, for example, where you phone up, you specify a sample, and you get it. ATCC would be the other one. I think what we're seeing here or what we're reflecting on is an oddity, if you will, in the existing reg. If all of the emphasis about human subjects is protection, why is public availability the criterion when it seems, as you can imagine publicly available stuff where there is and is not personal information associated with it. So if I call up ATCC to get someone thus and such, or Coryll to get a sample, I believe it's the case that most of those are stored in such a way that they are anonymous or whatever term we're using for anonymous. So the issue may not arise but it's certainly logically possible that there could be publicly available in the relevant sense—call up and get it, which also has personal information associated with that. And I think that's the ambiguity, well not the ambiguity, but what we're looking at here.

DR. SHAPIRO: Let's make sure we focus on the substance of this issue because that's a really very important issue. There are repositories which have publicly available under some reasonable definition of publicly available, as in footnote 3 on the page close to that. And the way the regulations are written, it seems to my understanding that these two criteria are not *and*, they're *or*? So you don't get the second protection automatically. You can only get it if you make an *or* rather than an *and*. And so let's try to focus on the substance of this and what the Commission feels that what is required in this case, one way to phrase it but not the only way, is an *and* here rather than an *or*.

MR. HOLTMAN: If that's the case, then we think the current reg is in.

DR. SHAPIRO: That's right. Alex.

Professor Capron: Well, I think that although they disagree, that Steve and Alta are on the right track when asking us to say what is the interest that is implicated. And if Elise's examination showed Steve that all those repositories that were publicly available met one of two criteria, either the data stored was anonymous or the data was stored with identifiers and explicit informed consent from the individuals involved that they knew that the study, that their identifiers would be there and it would be used for research involving anything about themselves, the kinds of concerns that we have would largely be met. I don't have any basis for knowing if that's the case, and it seems to me that although Alta may be wrong in that the regulations are exclusively talking here about samples and specimens and so forth, my suspicion is that the kinds of concerns that motivated people in having the regulation make this exemption, was not to burden research where people are dealing with material which a reporter could call up and get or anybody else who is in the position to publicize information. This is not information which people would regard as confidential. And that takes us back to Carol's basic point which is the information is being, the developer doesn't exist. It's not as though you would, if you were a reporter, could call up and say I want to know if they are at risk for this disease or not. And so it seems to me that the present regulation is inadequate in addressing the issue and if there is any reason to think there are repositories which meet the criteria of, you have access on demand, I guess that is the only criterion that's offered, that's to say, there are no particular restrictions in getting access to it, that it isn't enough and it ought not to be enough to say that as to information which doesn't yet exist as information—it is there in a biological sense, but it's not there in any sense that anyone would have been concerned about previously—that it ought not to be enough to have *or*. And I would put forward there for the recommendation that we would urge a modification as to biological samples and specimens, human biological materials, to insist that they are publicly available **and** will not be used in such a way that they could be linked to an identifier.

DR. SHAPIRO: Well, let's just see what the response is.

Professor Capron: My point is, that I think that it's consistent with what I would take to be the intention behind this, whether or not Alta or Steve is right about the exact history.

MR. SHAPIRO: Alta?

MS. CHARO: I'm interested in what you've suggested, but I still feel uneducated enough to make a recommendation at this time. I'd want to know more—in some ways exactly what Rhetaugh was asking and maybe, Steve, you could help by talking more about Coryll, maybe OPRR can help now or through written responses—about the number of situations in which we have samples that meet the definition as it's currently interpreted and how they came to be that way. Was it a case of where samples were collected, for example, surgical waste, and that for one reason or another a repository chose to then make them available without payment and without restriction to members

of the public. I mean, how often can that actually be happening and why should it be happening to understand whether or not there is...the interpretation says, "unrestricted availability subject to limited quantities and/or related costs." What I mean is noncommercial. I understand that related costs means you can be asked to reimburse for the actual costs of handling the material by the repository but they're not doing it commercially to sell it for a profit.

Professor Capron: I wouldn't agree with that. I would simply say that unrestricted does not mean that anyone can just get it because they asked for it. There can be processing fees, there can be charges for the materials. But there are no restrictions on a member of the public getting it.

MS. CHARO: Right. That's just what I said.

Professor Capron: But a commercial outfit that sells the materials, that doesn't restrict your access.

MS. CHARO: This is an interesting point.

Professor Capron: Unrestricted on demand, to me, the reason that there's that parenthetical made perfectly good sense. It means that you can't just say send me a hundred samples, thank you very much, by return post. They may say, well fine, send me a thousand dollars.

DR. SHAPIRO: I think two things. One, although it's interesting from some other perspectives, I don't think it would help us clarify this by wondering whether the cost is for a for profit or nonprofit organization and so on. But secondly, although I think the information that you are requesting is interesting, we should try to find out about it. It's not clear to me how that would change anybody's mind about it in respect to this proposal. That is, if we feel or if members of the Commission feel, that for reasons Carol explained that I'm not going to go over, that it really is inappropriate, that just the availability of it would make it—in a sense, publicly available here—is just not adequate protection, if there are identifiers, for example. And, the information request—I would like to know as well. I'm not quite sure how it would bear on the question. Could you help me with that, maybe? Maybe I just misunderstood.

MS. CHARO: I feel very insecure about making any recommendation at this point only because if it is this hard to understand the meaning of related costs or the meaning of unrestricted or the meaning of public, I can't begin to have a clue as to what this whole section is actually referring to. I don't want to shut down a research venue that might actually be benign until I know what it means.

DR. SHAPIRO: Bernie.

DR. LO: I think we have a problem that has heretofore been unnoticed, but I think I'd be very careful. First of all, if we start to recommend rewriting this part of the

regs, it actually affects a lot more than research with biological samples. I mean, as it's written, it's existing data, medical records, foods, questionnaire tapes that are generally available, so I think we have to be very careful that we're trying to fix a problem that we think is particularly important for DNA testing on stored samples, that we don't also undercut practices in quite different kinds of research. And second, I would just like to say for number one, the fact that it is publicly available means that anybody can get it. If you weren't a researcher, you could get it but if you were a researcher, now you can't get it is paradoxical. Now my final point is, I think that if we're going to fix it, it isn't going to be easy to fix because Alex spelled out that what we're really saying is, is it legitimate and appropriate that it's publicly available. I mean, outline some criteria having to do with consent...so that we should decide whether we want to just call attention to a potentially serious problem that we really haven't done much more than just say, look, there might be a problem. Or do we really want to go the distance of just try to rewrite this one little part, which I'm not sure is the meat of the rest of our report. It's not going to be easy. We could get really hung up trying to fix these two.

DR. SHAPIRO: Could I say a word about that? I don't think we should think of ourselves as in a position of writing regulations. Regulations will have to be written with great care no matter what we recommend, but if we still could recommend something here, a principle, by which we think the reg should be changed. We won't have to write the change itself. I agree with you that we'll have to be extremely careful and it's a very tough job itself to write the regulations. But it seems to me that if there is an issue here which the Commissioners feel is important, that we should find some way, without knowing exactly what the right way is at this moment, of focusing people's attention on it and perhaps recommending a consideration of a change in regulation of something of that nature. But I don't really want to write the regulations. We're not competent to do it sitting here and, as you say, it's a complex issue. We just ought to focus our attention. I want to bring us back to the issue just to see what Commissioners' feelings are, and then we can go about—not right this second but sort of producing language and so on. On the issue which, as I understand, it is that public availability, reasonably interpreted, let's say for example, as footnote 3 outlines it, is something that provides inadequate protection to people who have provided biological samples either with consent or without consent. That's really the problem Carol raised.

DR. GREIDER: I just want to address two points. One was that I agree with Alta that it would be nice to know are there examples of the repositories where these are publicly available—to get the data. And yet I also would agree with Harold that that wouldn't necessarily change my view of how I would look at this because we're not just talking about things that are existing today. We're talking about things that might occur sometime in the future, and just because there aren't huge numbers of samples out there right now doesn't mean that it won't be different in the future. So that is one point. The other point is, to my understanding, all we're talking about is whether this even should be considered before an IRB. We're not talking about shutting down research. We're

just putting it into the IRB mechanisms so that if somebody looks at it—and I don't see that as a very high bar that we're even talking about establishing.

DR. SHAPIRO: Alex and Alta.

Professor Capron: I want to agree and make two points. We are talking about where the river splits, and the important thing is even under the existing regulations, the reason why there is an exemption, as I understand it, is not because people's interests are not involved and not even because people cannot be harmed by what happens to the information, but rather, in a way, in reflecting what Bernie said, it's that that harm is not something that grows uniquely out of research. It is a harm that is already there. If your criminal records are publicly available, someone could go and print them in the newspaper. The information is there and may be embarrassing to you, may be harmful to your life but there's no escaping it. It's right there on the public record. And I think that was part of the thought in the exemption, that we can't create standards here that are higher, not that there isn't an interest. I think Carol has done us a great favor by saying we've got to look at that split in the river and say is the right stuff getting down the way where there will be no further examination of it. Not that it has to stop. And I think that we can, consistent with what we say in the rest of the report about the interests that are involved and the needs of consent urge that this be narrow without writing the regulatory language and the same consideration operate here. Narrow the exemption as the information which in a real sense doesn't exist until the research occurs.

MS. CHARO: Again, just to emphasize why it is that are, I will probably abstain from any motion at this point until I've had a chance to think it through. Maybe I would think better with a second cup of coffee, I don't know. But I find myself thinking about other situations that might or might not be similar. For example, this morning on the *Today* show they have people lined up showing signs, there was even someone from Waukesha, my home state, right? Hi, mom, in Waukesha. Now once on TV, that particular footage, where they scan the crowd, I would assume meets the definition as publicly available, and over the years I suspect that more and more often we will have to look at all of those hundreds of people that they scanned and diagnose more and more disorders just by close observation that we couldn't diagnose today. The information is there but not available to interpretation yet, but in ten years, twenty years, thirty years we could—just like today—diagnose things we couldn't thirty years ago just from observing people. And if somebody were to do that research, they would take the videotapes of the last year's worth of *Today* shows and begin counting the number of people who meet certain diagnostic criteria and there are some degrees of identifiability because we know this person has a mom in Waukesha, right? I want to spend a little time contemplating whether I really want to say that this needs to go to an IRB for review prior to the researcher being able to do his or her magic on it. You're right, it's not necessarily a big deal to have to go to the IRB and have them say this is benign, but I just

don't feel comfortable rushing until I've figured out all the situations this is intended to encompass.

DR. SHAPIRO: Okay. Other comments. Again, we cannot rewrite the regulations now, but how do the Commissioners feel regarding the basic point being made by Carol, namely that there is something here that needs some attention. And it's not fully adequate as it stands, we have to think about how to do it and so on and I don't want to propose any motions about fixing it today but that has to be thought through more carefully. But that we focus some attention on that and try to see if we can't meet the concerns. I take it that that's something we should therefore try to do.

DR. HANNA: Yes, we will try to find out some more information in the next week.

Professor Capron: In that process, may I recommend that the present sentence, which has footnote 3 attached to it, be dropped and it would be helpful in the text itself to explain the OPRR understanding. The present sentence suggests two things. First, it makes factual statement for which the footnote does not provide any support. And secondly, and I agree entirely with Carol, it says that this isn't really a problem because most are not publicly available. The point is as to those that would be publicly available, not in most, whether that's 90 percent or 55 percent or something are not such.

DR. SHAPIRO: Arturo?

DR. BRITO: I agree with Alta. We need some time to think about this, but one of the things that I'm thinking about, having thought through fully, is what about the process that makes something publicly available? What are the potential processes that could make something publicly available and I think that would be key when we're looking at this.

DR. SHAPIRO: Other comments and questions? Yes, Steve.

MR. HOLTZMAN: The guidance we've got from OPRR here is the minimal guidance. It would be useful to go to them and go through cases and say what is and is not publicly available. ATCC, Coryll, those are paradigms of publicly available: pay your money, get your sample. And what about the NIMH collection? A federally sponsored—many investigators that get at it but you can't just say send me some of those samples. There's a range of instances here and many require clarification.

DR. SHAPIRO: Other comments and questions? Thank you. Just to remind you, we're heading toward the next italicized position, which occurs at the bottom of page 184. We can go directly to that unless there are some issues on any other pages that people would like to raise at this moment. Alta?

MS. CHARO: On page 184 in the discussion about group interests. I would urge that we more explicitly acknowledge the root interest issue and the kinds of solutions

that were discussed and rejected, such as obtaining community consent, community notification processes, and such. They're kind of buried in here and since this is the place we are in fact coming down in favor of individualized harm and consent only, I think we should be more open about it.

DR. SHAPIRO: Thank you, Carol.

DR. GREIDER: I just want to agree with that. That's one of the things I had starred, as well. That we had so many discussions of group versus individual interests and that sort of the driving issue and it really doesn't occur in this first section at all. In the second section on prospective, it *does* occur and I really urge more information, or more explicit discussion in that at the very bottom of page 184 before the italics.

DR. SHAPIRO: Bernie.

DR. LO: I would like to make sure that what we're suggesting is a regulatory requirement and what might be good practice, and I would urge us to say that under certain sensitive studies it would be prudent and praiseworthy and good practice as many scientists have already done, to obtain some sort of community input—to not make either/or, but to explicitly invite scientists to get some community input on the sensitive studies.

Professor Capron: An additional issue that we might try to bring out here and it might even lead to a recommendation, although it may be that this would come later on when we're talking about the future collection, is the notion of being more explicit with people as their samples are collected about the range of uses. We recognize that it doesn't make sense to say that I am consenting to something if you cannot begin to imagine all the particular kinds of things that we talk about the need for re-contact. But, particularly the wrong that occurs to a person if they indirectly participate in research in which they find abhorrent and, obviously research around abortion is an example of an issue that people feel very strongly about. We could at least put language in that talks about identifying the fact that they really have no control and that a wide variety of research could take place and just be sensitive to that. At the bottom of 183, it seems to me that at earlier times we talked about the notion of people being wronged even if they're not harmed and maybe I make too much of this as philosophical or legal differentiation, but I think it's worth, Kathi, thinking there in that last full sentence on 183 of saying that there are ways in which people can be wronged even if they are not harmed. That is, even if they don't suffer the kinds of things that we enumerate under our reason on pages 9-13 of 184 where we talk about insurance or employment discrimination. Those are harms, but there is a notion of being used even if you are not harmed, that may be upsetting to people. And we don't end up saying this is enough to stop research but when we are reaccounting it we should at least make a reader who wants to be sensitized to these issues aware there is an issue there.

DR. SHAPIRO: Larry?

DR. MIIKE: I didn't know when to bring this up, but I think that the first point that Alex made introduced it. In Chapter 4 there's a discussion about layered consent. But also in Chapter 4 it just sort of lumps together samples taken for clinical purposes and samples taken for research purposes, and I don't see any of that stuff reflected in this chapter. If you recall sometime back, I thought we needed to change the consent process for clinical samples. At least take the piece out that says I consent to research in some way. There's no distinction here. In the consent discussion in this chapter, it's not reflective whether the discussion was in Chapter 4 in terms of possibilities of giving various kinds of information for various purposes, and I really think we need to make a distinction in the informed consent process of clinical sample collection versus research sample collection.

DR. SHAPIRO: Okay, let's make sure we come back to that.

DR. MIIKE: Yes, there was just no place to discuss this. I was just trying to help.

DR. SHAPIRO: We do commit ourselves to come back and discuss that more fully because it is an important issue. Okay, other comments and questions in this particular area? Steve. Raise your hand, bang the table, or something.

MR. HOLTZMAN: Make up for the comments I didn't make because I wasn't important, right? I think Alex makes a good point about the "harm" point here or the "wrong" point. But what we might also do here since we seem to be talking heavily in theory about what one might envisage as a potential harm, is it worth noting that when we went out into focus groups, what we found was the overwhelming majority people we dealt with found that that was not really an issue. All right? That they weren't concerned. They had a certain vision of how it would likely be used and that it would be good for medicine, et cetera, et cetera. As long as they weren't harmed, they didn't have a sense of potentially being wronged. So I think we have a philosophical discussion going on here in these few paragraphs. Look at the nature of the language we're using but we don't seem to get back to some touchstones of about maybe what we found out. Maybe people don't think we found out anything or—

Professor Capron: I thought we agreed that those focus groups were useful for us in teasing out issues but that we weren't going to recite them as some form of touchstone, that is to say, a public opinion survey.

MR. HOLTZMAN: So I think, I think that's fair enough. So the question I would then ask is how stridently are we going to push the theoretical concerns here, and for those people in this room who have had a lot of experience actually dealing with people in these contexts, what have they actually found? Does that matter?

Professor Capron: I certainly hope we are not strident on this issue.

DR. SHAPIRO: I look at this, this particular issue, which will come up in different ways and different contexts here, I feel it would be quite important to provide a framework for readers to think about these things although they don't have equal importance in my own mind. That is, I think in this particular case despite the inadequacies of those groups in terms of information, I quite agree—there's no real information there. Nevertheless, my belief is that's probably right, but for other reasons, not because that focus group took place, but for other reasons. And therefore, we do need to provide some framework to go through this, so let's tick this off in their mind and then go on. Other comments. Again, there is an italicized observation on the bottom of page 184. Any comments, questions, concernings about it? Okay, this has to do with unidentifiable samples and the claim here is the potential harm that these individuals effectively disappear.

DR. DUMAS: Okay, that's assuming that we know what we mean by unidentifiable.

DR. SHAPIRO: Yes, we will have plenty of opportunity to look at that. Yes.

DR. BRITO: The only problem I have is that the word genuinely, for some reason, bothers me. I think that sort of creates a sort of feeling that it, it almost implies that maybe it's truly not "genuinely." I don't know. It just—

DR. SHAPIRO: If you knew what unidentifiable is, you wouldn't need genuinely. We're trying to make the point maybe too hard here.

Professor Capron: You want to drop that?

DR. SHAPIRO: That's right. We can try to go to some effort to define that carefully, so it ought to be enough.

DR. BRITO: And then we drop it then it would read right. It would practically—

DR. SHAPIRO: Right. We'll come back or have a chance to look at these definitions.

Professor Capron: The definition is on the page before. Are we coming back to it or—

DR. SHAPIRO: As it comes up in the previous chapters also.

Professor Capron: I mean this is a summary statement.

DR. SHAPIRO: Okay, as we go back through some of these other chapters, we'll pick up some of these things again. The next italicized comment or bold print comment, however the right way to describe that is, occurs on page 186, and has to do with linked materials and has a section on identifiable sentences. Questions and comments?

MS. CHARO: Yes, beginning with the explanatory material on the previous page 185 in the middle of the paragraph, line 12? We state in other cases the repository might retain enough about it.... And, I would just like to suggest that the way I am reading this, this reflects many discussions we've had. It is absolutely an expansion of the notion of identifiability beyond that which is currently in use commonly around the country and beyond that, which as I understand it, OPRR has insisted upon. And, I want to make sure people really want to expand the definition of identifiability that way because we've gone around this and around this. To do this means that we get into the problem of the kind of blurry categories. The easy, bright-line categories where things that had some kind of code or other obvious linkage, and this one is based upon essentially cell size. Being able to deduce from indirect evidence something about the identity of the source of the sample rather than using a code or link that was designed to make that possible. And once we are going to define identifiability through the ability to deduce identity, the classification of those people whose identity sufficiently deducible—I don't know if even that's the right word and those who are not becomes very blurry, and we've been around and around and around and I wasn't sure I remembered if there had been a clear consensus to go this way. If there is, I think we need to be very explicit in the recommendation which follows on the next page, that this goes beyond the current Federal, common Federal practice and interpretation. But I also want to double-check on the consensus about this.

Professor Capron: Is your concern met by the parenthetical at the end of the paragraph?

MS. CHARO: The parenthetical in the paragraph?

Professor Capron: At the end of the paragraph where in effect it says if the cell size, the group size is 10 and the results are 9 out of the 10 have the marker for rapid heart rhythms that will cause instantaneous death, if you are known to be in that group, you might as well be identified. Whereas if it's a thousand people and the results are one in a thousand...

MS. CHARO: But it's being used here...

Professor Capron: It's being used to bring it into a category of saying it doesn't automatically go over in the group about which we have no concerns, see our last bolded statement.

MS. CHARO: Right. I know. I understand that. It is, it is absolutely a big divide because once things are considered to be identifiable, we're going to have many more procedures we have to go through in order to evaluate their risk and the protections that are associated. And you're asking if I am satisfied by that last paragraph? No, because that parenthetical is about the—

DR. MIIKE: Can I jump in without putting up my hand, too, then if this the way this discussion is going to go?

MS. CHARO: Yes, you may.

DR. MIIKE: I'm asking for procedure. Do I have to put up my hand to talk or can I just talk?

DR. SHAPIRO: Well, it would be helpful if people waited to be recognized. It's fair and more appropriate, so let's try that, if people can restrain themselves. Larry.

DR. MIIKE: My understanding of what this discussion is about is—not that we're going to change the regs—that we want to make it clear that people haven't misinterpreted the regs. Isn't that the point of what this section is about?

DR. HANNA: Well, I think that certainly in the past year of discussing this, it has been apparent that there are various interpretations of what constitutes an identifiable sample. My understanding of where the petition came out was that coded equals identifiable. That was pretty clear from the Portland transcripts. The reason we added the parenthetical phrase was because it doesn't mean that you're jumping off a cliff essentially. There's a progression. Then you consider *how* identifiable. What's the probability that that person could be identified if you used that in your tabulation of whether it's minimal risk and then you move through the next steps. Does that mean then it can go to expedited review? Does it mean it you can waive consent? So, we tried to build a continuum of decisions.

DR. MIIKE: Well, I'm just looking at that sentence on page 186 about line 4, 5, 6 where you state that apparent from our discussions, that some investigators...so I'm looking at that and saying I don't see this as the way that this is being presented—that we're going to recommend changing the regs. It's just that clarification of the interpretation.

DR. SHAPIRO: I agree with that. Steve and then Carol.

DR. HOLTZMAN: Kathi, I don't think that next sets of issues you just raised about harm and whatnot really should infect this discussion. I think there has to be clarity as to what identifiable means. I think that's a bright-line test. Has to be, has to be set up. And I think how we get to this point in the discussion, is even though there's very textured language in the reg itself, readily ascertainable.... For example, OPRR's guidance largely seems to be if it's possible to create the link, it's identifiable. And we seem to have adopted that. If it is possible—we don't go with what degree and if what not. If it is possible, and if you take that as your standard, and I personally think it's a lousy reading of the reg, but I'll go with the Commission as long as we have clarity, okay? Then, how you come about the identifiability such as cell size is kind of irrelevant. It's either identifiable or it's not. Now one of the questions I asked several months ago is reflecting Kathi's point: we think there are lots of different interpretations out there. But

maybe we ought to go find out how people are actually interpreting this. Did we ever do that? Are we finding out that if we codify in our own recommendations an interpretation that says identifiable essentially means logically possible? Would that change a lot of current practices, which is your concern with the cell issue? Correct? Do we have an answer to that question?

DR. HANNA: We have several answers to that question. We heard from many people that there was confusion out there. I think we heard from Mary Claire King in Portland that she had interpreted the regulations in a way that perhaps was very conservative, and if you really tried to parse out her understanding, she probably misinterpreted it and maybe intentionally on some things. So, and I think we've heard from OPRR that in their view, there has been variability in both IRBs' and investigators' interpretations.

DR. SHAPIRO: Carol's next, then Larry.

DR. MIKE: I don't know, Steve. I think you're over-reading this language. I don't read this language to say that if it's possible to be deduced by cell size that it's identifiable. I think that what it's trying to clarify is that if there is a code there that can link it regardless of whether that is in a repository or research or et cetera, there is a linkage possible. So it's not as wide open as I hear you interpreting it.

Professor Capron: I think we need some clarity. I think Alta was right in highlighting this. We've had discussions each way. We're talking about a situation in which a repository has a list of the x number, let's say 100 samples, that it's sent over. When it "coded" them, it just numbered them 1 to 100 and it could not tell you if you provided the code and said I want more material on sample number 47 because it got lost or damaged in the lab. They'd say we don't know which one number 47 was. We can sell you all 100 samples again, however, if you want to start over in your research because we know which 100 we drew from but we don't know which is which. So it is that level of information and we know whose samples we have in the lab. In other words, it's not in our lab anonymous, even though it is to you anonymous. And we're saying no because they could tell you who the 100 people—Jones, Smith, et cetera, et cetera—who the 100 people were, who were in the group of samples, even though they can't link them, that still falls within some level of identifiable. I thought that sentence was quite clear in saying it, and I agree with the conclusion, but I think that Alta was right in saying this is something we have gone back and forth on. So, it's not coded in the way we usually mean, which is the name Capron is replaced with the code 721.

DR. MIKE: I think that we need to clarify that situation.

DR. SHAPIRO: I agree we need to clarify. I think we spent, my recollection, although I haven't read the transcript at all. My own recollection that "really possible" was the best way to define what position we came to whether we all liked it or not. That's where we came out to my recollection. We wanted to change our minds and so

on. It's my own view that that is probably the only way to write—if you want something clear, it is almost the only way to do it and provide the protections. And I want to repeat, once again, that this is what people have already said a number of times this morning, all that's happening here is that we're creating various streams down which particular protocols go depending on the harms that are exposed. If there's a harm that's possible or a wrong, is it possible or not possible for that to happen. And if it's possible, somebody ought to at least not rush by this. And therefore, that's the line I draw. Whether it's a good interpretation of the regs is another matter altogether, and Steve may be right about that. But it seems to me that's where we could draw, if it's possible to go back to the person, it's possible then that these harms and/or wrongs and with whatever else we are concerned with will happen and therefore, someone ought to think about this. If it's minimal risk, it's a very simple proposition. If it's not, it ought not to be simple. And that seems to me to be straightforward. I think that's what, I don't know, Kathi, now you tell me, was that what you were trying....

DR. HANNA: I think we were trying to reflect in that parenthetical phrase that there's a continuum of identifiability, that within the category of identifiability there is a continuum based on probability of identifiability. And that that probability calculation enters in when you get to the minimal risk section. So we introduced the notion there just kind of to forecast that it's coming up later, so that you're not, as I said, you're not making a final decision here. You're just pushing the protocol into one direction.

DR. SHAPIRO: We're not throwing the weight of all the protections that are possible into the hopper just because it's...Bette?

MS. KRAMER: I also have not gone back and reviewed all of the transcripts but my recollection is a little bit different. I did not think that we as a Commission had come to consensus on the example you just cited, when the repository knew what 100 samples they had sent, but they did not know, they themselves could not match up any particular sample with an individual. Now I know that the gentleman from Mayo said they regard that as identifiable, but I did not think the Commission itself had adopted that definition of identifiable. I thought that we, we're still talking about that calculus and I don't recall that we did adopt that. Kathi, I'm sure you studied those transcripts, didn't you?

DR. SHAPIRO: There are people that want to talk. I don't think we adopted it in the sense that we had a formal agreement but it's before us now and we can decide right now where we want to come out. Bernie and then Alta and Tom.

DR. LO: It seems to be that this an issue which we've thought a lot about and talked a lot about, and we don't have consensus. All investigators and IRBs need to be aware of these arguments. We didn't reach agreement. It doesn't really matter right now because the regs already state you get expedited review or full review, but I think conceptually it's important because to the extent that anybody changes policies later

using identifiability as the branch point for a very different set of issues, then what gets put into which stream becomes more important.

MR. HOLTZMAN: I don't think it's expedited versus full. It's whether or not you have human subjects research. That's why I think we need a bright-line test, because there is a lot at stake.

MS. CHARO: I think that part of the reason why I've been having so much difficulty coming to a conclusion myself about how I would like to see this problem handled is that there are two distinctly different spheres of consideration. One is a matter of principle and pure logic. As principle and pure logic we're absolutely correct that it's a continuum of identifiability in which this kind of example of cell size falls on one end of identifiability through deduction, and where obvious explicit codes, it falls at a different end. As a matter of practicality, however, I think that we are talking about very different beasts and it's for precisely the reason Steve just mentioned. If we recall that the research review process begins with a self-referral by an investigator to his or her IRB, presenting him- or herself to this committee and saying I believe I'm covered by the research rules and I'm asking for the requisite review—subject to lots of influences by the department chair, by journal editors in retrospect and et cetera but it's fundamentally a self-referral process. It argues for a system of rules that are easy enough for investigators who are not spending all their time thinking about regulations to know when they are or are not subject to the rules and when they do or do not have to go to the IRB. This is why at the level of practicality one might want to have bright-line distinctions that don't follow the continuum of logic and principle simply because of the level of workability. We might achieve higher levels of compliance when compliance is simpler. Now, as a body that is supposed to be doing ethics in a governmental context, I struggle with whether our duty is to identify the kind of ethically purest way to go and leave it to the regulatory people who will interpret this to then ratchet it back to something that's more workable or whether we should incorporate that concern from the very beginning. But at a minimum, if we continue to take this definition and use it in a way that emphasizes as a principle the notion of identifiability based on any possible identification by any methodology, codes, or deduction, we should at least openly acknowledge that this may not be workable in practice and that some balance between an idealized system of protection and a workable system of protection may have to be made at the level of changes in the wording of the regs or the actual OPRR guidance that goes out to the IRBs following our report.

DR. MURRAY: I thought I knew where we were until I just heard Alta. But let me just give you my crude version of my understanding of it. I think I was one of the people from the beginning who insisted that this continuum actually, that the ends of the continuum were very different in terms of what they engaged in both conceptually and how easily identifiable somebody was. But I've become convinced that the current structure is a sensible one, and abruptly here's how I see it. You've got the conceptual

distinctions and the ethical considerations, and they look like this. And you've got this policy apparatus, which is a totally different sort of being and there's no way to make them fit in a precise manner. So what you want to do is ascribe a certain virtue. You want to make it easy to follow, simply you want to catch all the relevant cases and so the rules you are going to set up are intended to solve this set of practical problems on the policy side. I think if I understood what Carol said a few minutes ago, I agree with it that this approach does seem to be a reasonable response and allows us to capture most of what's important, conceptually and morally. Even if it doesn't capture it at the first level, it may capture it later on when we consider whether it's minimal risk or not. I hope that if I've got that wrong people will straighten me out.

Professor Capron: When I had my hand up and was called on before, I was going to make another comment, and Larry's question caused me to divert on that and now Alta's comment makes me divert. I agree. I have two comments. The one I wanted to make in response to Alta, I agree, Alta, and I agree with Tom's gloss on it that it is a virtue to have something that is implemental. I don't see the problem with this recommendation being easily implemented. If I'm on an IRB, I know two things. Researchers, I've got to rely on researchers asking for permission to do their research. I mean, that's the whole superstructure of this important system. Yes, there are going to be penalties on people like Martin Klein who go off and do it without any consent. That can happen and does happen. But what is likely to happen here, is the person comes forward with a protocol and says I believe it's exempt. If I'm on the IRB, I have developed a very simple form for such studies, and it asks several questions. Will the samples be coded where the code is linked to an identifier that is for a particular person. Or, will the repository draw from a sample that is identifiable and be able to identify the members of the sample? And once that becomes known that that's the question I am going to have to answer, I may not know the answer. I may have to call up the repository if I'm not a researcher and say are you going to keep a record of the samples you send me? They say yes, we always do and you can tell who, particularly the names of the people who are in that or are your samples anonymous to start off with? They say they're anonymous to start off with, I can check "no" in that box. No, there would be no linkage to identifiable people and if they say yes, then I have to say yes. And at that point the committee is going to say we can't exempt it. We now have a process of other things we look at to see whether it could be expedited or whether consent is necessary, et cetera. But it's a very, I don't think this is complicated. I think it is a fairly easy bright line. I like your criteria and virtue, as Tom calls it. I don't think it's a problem. The comment that I was going to make is right before the recommendation, the sentence beginning on line 7 of 186, and I'm going to turn to my colleagues like Steve and Carol and ask them whether my sense that this doesn't quite capture what's involved. This says that the issue of identifiable is further confounded by the researcher's growing ability to identify the sample even when unidentifiable. And then it goes on to say because of the uniqueness of clinical information, I thought what was growing was their ability through

finding genetic markers and so forth to be able to say the sample we have here turns out to be Eric Meslin's sample because we know with his genotype over here and we know the sample. It may be that there is also, but not growingly so, clinical information. I would add therefore, the uniqueness of the biological sample itself or of the clinical information that comes from that material. And do my scientific colleagues, wasn't that the point that everybody kept making, which is the irony is that we say that this is unidentifiable but the very process that we're engaged in looking at is one in which that change--is that right?

DR. LO: Like Alex, I have a two-pronged comment. To just follow up on the last comment by Alex, I think that in addition, another way in which apparently unidentifiable samples get identified is through fancy computer techniques that allow you to use census data, phone book data, and so forth just from very apparently scant demographic information, go back to who the actual individual was. So I think there are a lot of ways that we're talking about and we might want to highlight them all. The comment that I wanted to make and I really want to get back to is my confusion over what's at stake here because, when I look at chart X and chart Y, I think of two different ways in which identifiability enters in here. Chart X, identifiability comes in as to whether it is even considered human subjects research, but my reading here is that it's not may be identifiable but may be readily ascertained, so it's not identifiable in the sense we're using it. It's associable in regulatory language and seems to me is different according to the footnote. Is that not a correct reading of the reg or does it say identifiable? I need to defer to Alta or Alex. Because where the term identifiable link comes up apparently has to do with whether it's eligible for expedited or full review. I think again it's an issue of logically what do we mean but also what are the consequences of the protocol.

DR. SHAPIRO: I think that question comes up in chart X, just one second. I apologize. Your question, Bernie, on the issue of how it comes up in the definition of human subject.

DR. LO: It's not just is it identifiable but is it sort of readily identifiable. Why is identifiable possible versus likely? It seems to be the same term is being used with different probability weights depending on what the branch point is.

Professor Capron: Isn't there an error in the chart X, by the way? Before we discuss it further, on the right-hand column coming down from the phrase "are those data or specimens publicly available." No, it shouldn't be. You need two different boxes. You have a "no" box coming down from "will the information be recorded in such a way that it can be linked. "No" leads down.... Does everyone see where we are?

DR. MESLIN: We have it on transparency, if that would help.

Professor Capron: Well, maybe you should put it up.

MS. CHARO: Bernie, it's usually the rule that where words are different they're intended to mean different things. But the interpretations at these various places in the regs, the interpretations given to all of these phrases on the subject of identifiability have been the same, and it's made me wonder because ordinarily you'd expect there's a reason why the language differs and there's an intent to have different rules apply to different levels, but that's simply not been the case in practice. So that our discussion about what constitutes identifiable, the possibility of identification, is one that is key to whether or not an investigator is obligated to present himself or herself for review by an IRB as well as coming up in other contexts. And so, right, it's very confusing because it's surprising to see no use made of the different language, but I have no knowledge of the history of the drafting of those regs and whether this uniform interpretation at every level is consistent with that history or not.

DR. LO: The star at the bottom of the page says that identity of the subject used in...

DR. SHAPIRO: This is chart X?

DR. LO: Excuse me. Chart X. Now the big star with the two footnotes at the bottom. That is the second one that's incorrect? Is that what I hear you say?

MS. CHARO: No, I'm not saying it's incorrect. I'm simply saying that again, to my knowledge, and I happily stand corrected by people in the audience who know this better than I do. That the interpretation of identifiable up until now in practice has been samples that have codes, links, et cetera. That deduction from cell size have not been used as a form of identifiable, has not been interpreted to mean identifiable in practice up until now. And that this notion of identifiability has been used consistently throughout the process no matter where you are, whether it's at the level is there a human subject or the level of is this research exempt. Therefore, our discussions need to take that practical matter into consideration. That's all.

DR. SHAPIRO: Steve, first.

MR. HOLTZMAN: I just want to throw my support a hundred percent behind Alta. What's taken place, what's striking is it's very textured language, different in different cases, and yet it seems consistently the answer is effectively a standard of "possible." Basically, I think except for the cell point you're pointing out, it's a natural extension to say that if you move down a path in which at every layer you basically say, is it identifiable and it's natural to then ask the question, other modes of identifiability you haven't considered before, beyond codes. Okay, now that's what puts us on that logic train where Harold ends, where I think the Commission largely has come to. And I think these charts are actually very clear. I mean you could spend a lot of time—it works. These charts work.

DR. SHAPIRO: It seems to me that if we use the criterion “possible,” I think it has tremendous advantages in the point of view the way we deal with the material. That is, it’s clear what you’re saying. You don’t get caught up in words or how to define or it’s readily available, not readily available, what it means, what cost means, so on and so forth. It just says if it is possible or not? And as Bernie has pointed out, there are all kinds of ways things are going to be possible that we haven’t thought about because we can’t think them all out right now. But it seems to me to lead us into a pretty clear framework. Now we could decide at the end of the day, once we accumulate all this, that using “possible” is unworkable or is so costly to some other valued activity we want to pursue that we want to make some compromises. Now I’ve not seen any evidence yet that that’s really going to be the case. If we’re, to me, I still don’t really care how people get identified, either they get identified or they don’t. And the harm to that person, I understand it’s probabilities, so that if you would have cells—not 1 cell and not 10,000 but 378, versus 78 which changes the probability of being identified. And we talk about risk, you have the harm of the standard calculus that we all go through. But that can all be dealt with, within the system, within this framework, with people making sensible decisions as they go along. But if we have to, it seems to me, the hardest decision we can give an IRB is to decide what identifiable is if you don’t use “possible.” Then you really have a problem because there’s all kind of identifiability. It’s like this minimal risk all over again only you’ve introduced it once more for, I think, very little gain. Bernie?

DR. LO: I actually agree with that completely. I’m just concerned that when I read the section of the reg, apparently what we’re advocating something different from what the regs say. Then we’re back in our problem. First thing we say is that we like the regs and now we’re finding little places....

Professor Capron: We’re explaining—our understanding of what you just said is when it says the identity of the subject is or may readily be ascertained by the investigator or associated with the information. We are saying that means it’s possible to do so. One such example of possibility is...

DR. SHAPIRO: To me that seems to be, of all the things we talked about, the clearest and also satisfying in some sense, unless we find out in the end we produce an unworkable...

Professor Capron: OPRR or the Interagency Committee ought to make clear that this language means it is possible. For example, when a repository keeps a list of the samples that it sent over. And I don’t think we have to, if that’s the case, do statistical studies to say well how many people are like the Mayo Clinic who already read the regulation that way, and how many are like Mary Claire King who reads it her way, and how many and somebody else reads it a different way. We’re just saying this is the reading that we think is the most congruent with the interests which motivates the whole set of regulations. I endorse that view and I hope that we can finally resolve this and move on.

DR. MIIKE: I think that we are going to need a little bit more explaining because the plain meaning or “readily ascertained” is not “possible.” So I think we need to talk a little bit more in our discussion about how circumstances have changed in the ability to identify people compared to when that language was drafted.

DR. SHAPIRO: I think that’s a good point. It’s not only readily available. That’s not the only phrase there. It has an association with them and I don’t know, it depends on how you think about that phrase, but I agree with the point you’re making in this.

Professor Capron: Well, I don’t see the purpose. Larry brought it up before. Are we rewriting the regulations? No, we’re not rewriting them, but we’re urging that they be read to mean the following: Because they could mean we’re giving our sense of the meaning not as an exegesis of the text itself, but as going back to the policy that lies behind all of this, in light of the changed circumstances, the greater ability to make much more use of what was just a lump of tissue in a paraffin block or something.

DR. SHAPIRO: Okay, we will take a run at this in that framework and see how it comes up. Let’s move on. The next section of this deals with criteria for expedited review, and in fact, there is an insert which is, as Kathi referred to as an italicized line on page 189, lines 11 through 13, which has to deal with “special scrutiny” studies and the material leading up to that. And if you turn the page over to 190, there’s another one of those phrases which has possible recommendations. Kathi or Eric, do you want to say anything about this particular section and the possible recommendations?

DR. HANNA: Well, to lead in to that, I want to explain about what staff was thinking was here, and I want to thank Andy Segal who is sitting in the audience for helping us work through some of this. When we were trying to talk about minimal risk, and then also, I am going to throw in here the rights and welfare criterion, which is also one of the considerations. We were trying to separate out those two categories—minimal risk, rights and welfare—and understand what they mean in terms of interpreting the regulations. We went back and forth a great deal on this. One of the things that fell out of this, and I think Bernie helped in some e-mail that he sent, was this issue of—and again it refers back to Alex’s concern about harms and wrongs—that there might be some categories of research that an IRB would struggle saying it is actually above minimal risk, but perhaps might fall into the area of concern about people’s rights or their welfare and Bernie, I think, used the phrase “special scrutiny.” That there might be some classes of research that fall into a special category where risks might **be** minimal, but other concerns might not be. We’re trying to grapple with that, and Bernie supplied some examples that show up on page 189, in paragraph lines 7 through 13, as some examples of research in those categories, and I think we just need to think about that more and staff certainly needs your help in trying to figure out how to actually define that. If we’re going to talk about special scrutiny categories, we need to be very clear about what would fall into those categories.

DR. SHAPIRO: All right, I have some questions but let's go to others. Alta.

MS. CHARO: I'd like to discuss this section which grapples with minimal risk. I feel like I can only do it if I talk about the rights and welfare language. Just as an organizational point, it might be that we should consider flipping the discussion so we start with the waiver of consent when minimal risk and right and welfare are both implicated, and then move on later to expedited review because it will allow us to have integrated discussion of minimal risk and rights and welfare. At this point now because they've been separated. I just want to share with you an e-mail exchange I had with Kathi because I would like to put it on the table as possibly something for us to consider. We were going back and forth on what rights and welfare might possibly mean. And I said, well here's a speculation that minimal risk really is more concerned with invasive research and focuses more on physical risks. And that rights and welfare is about the psychosocial problems that we've all identified, the problems of stigmatization, insurance discrimination, employment discrimination, etc., and that one might find that this actually creates a sensible division in this language. And that, therefore, when you talk about the risks of daily life, we're talking about the risks of getting a broken arm or the risks of being run over by a car and that you then measure what happens when you go into this research study and somebody's going to stick a needle in your arm and you say, is this more or less than what happens in daily life. Because we've all acknowledged that psychosocial risks are particularly difficult to measure as against daily life. And then Kathi e-mailed me back subsequently to say well, actually, we've got the following interpretation from OPRR, had nothing to do with this possible separation between physical risks and psychosocial risks. And yet I still find myself circling around and wondering if, regardless of whether then that's the current interpretation, whether there's possibly some value in trying to separate these two categories of risk a little bit because the difficulty in comparison and measurement for them—I know we went around this in Portland, I think I remember doing it with Alex—I still feel like the measurement problems are qualitatively different. It also admits of the following possibility: The minimal risk category, as was gone over in perhaps incredibly enthusiastic detail here, is one that looks at physical risk relative to what you are already experiencing, and then says if it's no greater than what you're already experiencing, it's okay to do this research without further consent, subject to the other criteria. The rights and welfare language doesn't make a comparison to daily life in any fashion. It simply says, "adversely affects people's rights and welfare." This struck me as being important in the psychosocial area because of a point that had been, I forget where now, about whether even if something is within the realm of what people experience in a daily life, it is justifiable for us to thrust more of it upon them. So even if I face the possibility of discrimination every day of my life because I'm shorter, I'm curly-haired, or whatever, is it really right to thrust yet another possibility of discrimination upon me? Another quantum of it? And then by using language that simply says "adversely affects rights and welfare," we don't have to worry about whether or not it's consistent with what we're already going through, we get to

simply discuss de novo at the IRB, whether it is something that we think of as being harmful in some fashion. And so I find myself wondering if there might be a new way to use minimal risk versus rights and welfare that might help untie this knot. As a final comment, as it now exists when I read the rights and welfare discussion that comes later in this chapter, I found it extremely difficult to distinguish it from the discussion of minimal risk that had preceded it, which was simply kind of performance art of the problem.

DR. SHAPIRO: Thank you. Eric.

DR. CASSELL: This has a quality of “sticks and stones will break my bones but words will never hurt me.” And I call to mind two studies in the social sciences which bear on this. One was the famous men’s room study in which people were exposed...there was no physical harm involved at all, but people were horrified at what that study did. And the other was one that was done in which people thinking that the subject was in pain kept causing more pain because the investigator pushed him. Leaving aside the validity of the findings, that’s a different issue entirely. Both of those things exposed people to a kind of risk which was greater than everyday life. In fact, everyday life is set up to avoid those risks. That’s the way that society sets its world up. So I don’t find the distinction here, as in a lot of other places, between physical and other than physical risks to be a useful...

DR. MURRAY: Eric has referred to two studies, Humphries’ study published under the title “Tearoom Trade,” of anonymous sex in men’s rooms in...I forget where it was, in parks and things. What people thought particularly horrifying about that was that Humphries took down the license plate numbers of people, and he then disguised himself and went to their homes, tracked down their addresses, and went to their homes to get information about them. So part of it was that the anonymity didn’t exist, he breached it coldly. He did not publish the names of his subjects, but he knew who they were, and without their consent. He got information at home but also observed them and linked information. The Mulgrom stuff is definitely human subjects interaction. In some of those conditions, the experimenter required this “subject” who thought he was the experimenter, or she was the experimenter, to actually hold the subject’s hands down in some electric shock apparatus. So that was no mere observation study, that was very much a deception and manipulation study. I’m reflecting about Alta’s desire to distinguish the psychosocial from the physical. It can be difficult to weigh the psychosocial, I agree. But I’m loath to introduce another layer of complexity in the analysis of it. I also didn’t agree with your comment that the discussion of minimal risks, if I understood you correctly, seemed to be a distinguishable from the discussion of rights and welfare. It includes expressly, lines 11 and 12 on page 192, “The subject may be improperly denied the opportunity to choose whether to assume the risks.” That’s quite different from the definition in my understanding of minimal risk. I have one difficulty with the passage of minimal risk, primarily the stuff that begins on page 188,

from line 12, and goes through that paragraph. It seems to me to be needlessly confusing and negative and almost apologetic. I would put it much more positively. I would say something like, “yes, insurance discrimination and the loss of access to insurance would be a harm of considerable magnitude.” How likely is that in a study that uses human biologic materials? In most cases it’s less likely, or no more likely, than inadvertent release of one’s medical records. So if that’s the sense in which it is a risk.... That is, it’s not zero but it’s real low. Therefore, it’s something I think we need to explain that rather differently than we explained it here. But I’m not convinced that we should make special provisions for psychosocial risks. I’m open but I’m...

MS. BACKLAR: I think that some of the same problems that are obtained here, with all the struggle we went through about minimal risk in the capacity report and that is the issue that’s being brought up, Alta, and I’m still very stuck with. And initially I thought that we would look at this differently because we’re looking at an inanimate object and a person who’s stealing things. But I’m beginning to consider...I thought perhaps it didn’t obtain in the same way. But as I think about it, particularly thinking about Mulgrom and the Humphries “Tearoom Trade” and so forth, I’m seeing that it really does obtain. And I’m very concerned about that everyday risk, which we might pile on people who have that everyday risk, I’m thinking about groups of people who might have a certain ethnic attribution or a certain diseased population. Just because they have that, we consider that it’s okay to do this because they’re exposed to this anyway, and we are then putting that much more risk on a group of people, a certain group of people, where we might not put it on other people. So I’m still...I think the same problems obtain here in how we identify minimal risk.

DR. GREIDER: I like the rewording of some of the language on page 188, lines 12 on. And I’d like to add one other thing that disturbs me about the language that is there, and that is it seems to me a very circular argument to use an example of medical records as everyday life when we’re talking about information that will go into your medical record. That I think if we’re going to use something as an example out there as what is minimal risk, we should avoid the issue of medical records entirely because we’re talking about information that’s going to go in there. And that circularity does not make me comfortable.

Professor Capron: I very much endorse Carol’s comment. Let me put it...a different spin on it, as it were. I think if the concept of ordinarily encountered in life makes any sense, the notion is, without one’s consent, just like deciding to get up in the morning, go out in the world, you encounter certain kinds of risks. Now, where you go beyond that and you are seeking medical care with your consent, there are risks that go with that. We have now put on the table that in that kind of situation, those are things which you would be told about the risks are, decide if they’re worth taking under the circumstances, and so forth. The whole point of the minimal risk discussion is potentially to exempt the process from that consent. And so for an additional reason, not only does

the very category of information you may put the information into the medical record, but the content of the medical record is having faced a potential illness, I make the choice that it is worth running the risk that my record will now say I have a disease which will make me uninsurable because getting treatment for that disease is today more important to me than that risk—I'm making a balance. Whereas here we're talking about something that is outside the context of consent. And it seems to me that for that additional reason it's not a good analogy. That said, I'm not sure that we have another analogy that leads to the statement on line 4 of page 189 that most research on biological samples must be deemed minimal risk. And if that's the case, that the reason this example is in here, although it ought not to be, is that it is the argument which makes the case that, hey, all this is minimal, then more important than removing the example is rethinking the conclusion. We go on to talk about, "however," the next paragraph in effect begins, "having said that." So you know, if what we're saying is on the face of it as an initial matter, compared to having a physical procedure done on you where your life could be at risk or something, these kinds of things strike us, initially, as not being in that high-risk category. Let's not reach a judgment on that until we consider some other things.

DR. SHAPIRO: Larry.

DR. MIIKE: Just a problem I'm having with this whole idea about minimal risk as currently being discussed and as apply in the other areas is that we're dealing with tissue samples, we're not dealing the human beings themselves. So talk about the risk of everyday life—What life? So what are we comparing? So it's more of a rights and welfare of the individual that is at risk in any other concepts that traditionally associate with direct human research subjects. So I think we're sort of having the wrong discussion here. I think we should just look and say, is this an applicable situation? My tissue doesn't feel pain, my tissue doesn't feel embarrassment. So I just think the discussion is sort of off in talking in traditional contexts and what this minimal risk issue has been applied to in the past. I think we should just sort of say it right off.

DR. SHAPIRO: Okay, Steve.

MR. HOLTZMAN: I guess the way I think about that, Larry, is you are working on tissue so you're not going to hurt the tissue the way you could physically hurt someone. But the nature of the research is it's generating information.

DR. MIIKE: I agree, but I'm saying the whole concept of minimal risk and the issue about the risk of everyday life is inapplicable.

MR. HOLTZMAN: Well, except that the way I think it through is that what is the risk and is it more than minimal in terms of the generation of the information. That's the way I frame the question. The generation of the information, does that create a risk which is more than minimal? And therefore, I'm not sure I agree with people that we've got a circularity here because I think it's proper to say is the information generated in a

research study qualitatively different than, more risky than, that which is generated in a routine medical exam and gets recorded in a medical record? So I think that is important, all right. Larry, you look puzzled. Remember, research results are not recorded supposedly in your medical records, okay. So a proper comparison is to ask the question, am I generating information that is more risky than that which is generated in a routine medical examination? So I think that is a proper question to ask. And then the second thing is I think in terms of yes, going out into the world of everyday life, but then you have to fill in that context. When you get out into the world, there's a lot of information that's part of your being in the world a certain kind of society. And I sent an e-mail out over the summer on this subject; it was an example of that. And so if I were writing that I would want to contextualize the question of is there minimal risk in generating this information from a study of the tissue that's qualitatively more risky than the kinds of information that generate in everyday life and the kinds of harms that come from it? And secondly, that which is generated from a medical exam. That's the way I frame it for myself.

DR. SHAPIRO: I guess it's the word "routine" that caught my attention.

MR. HOLTZMAN: A diagnostic exam.

DR. SHAPIRO: Well, okay, but routine means to me, at least I interpret it that...

MR. HOLTZMAN: A PSA test that most men get, which is predictive of prostate cancer.

DR. SHAPIRO: I agree with the premise you made that it's really the information that we ought to be focusing on; that is important. And it's the risk that that information contains, could contain, that we ought to focus our attention on. I'm just trying...but I also appreciated the point that Alex made that certain types of information in a medical record have some implied consent. You decide if you want that in your record, okay, because otherwise you tell your doctor not to give you this exam, or you won't take the exam. And there is some consent implied in it. There might be certain types of medical information which is really not so formalized, where the analogy might hold a little better, but I want to think that through some more. But in any case, let me go back to my list.

DR. MURRAY: That's a very creative use of the notion of risk encountered in ordinary life. And where the medical record fits. And if I stand back and say, well, what are the risks in everyday life associated with me having a medical record at all, even a medical record that doesn't deal with any episodes of illness, simply with having a relationship with a physician, a possibility that that record will fall into someone else's hands whom I don't want them to have it, and they might even make use of it to hurt me in some way, that's a possibility. I hope it's rare, that it will happen rarely if ever. It's probably less...it's probably more of a danger than most people realize, as Alex pointed out. But it seems to me to fall within the definition. And remember, as I read the reg,

lines 3 through 6, it says—by the way it includes both the words “ordinarily encountered” and “routine,” they’re both in there—says “probably and magnitude of discomfort, anticipated in research, are not greater in and of themselves than those ordinarily encountered in everyday life, or during the performance of routine physical or psychological examinations or tests.” I think I would be comfortable with offering as our interpretation of these regulations that information which would be routinely gathered in the course of medical care and entered into the medical record, that the information gathered in the course of the research is no greater risk and is not more likely to be exposed than any risk that would be encountered in everyday life. Maybe we disagree about that. I need to be shown why that is wrong. I mean when our family physicians at our university do their initial visit with you, they do a genogram, for heaven’s sake. By which...I don’t understand exactly what a genogram is, it’s basically kind of a very extended family history of disease as well as those other things. There’s a lot of genetic information in that record per se.

MS. CHARO: First, just as an aside, having heard about this tearoom, is that what it’s called, the “Tearoom Study”? It made me think back about the discussion about publicly available data and wonder how that would be played out onto that portion of the regulations.

Professor Capron: It wasn’t existing data, Alta. He collected it.

MS. CHARO: I was simply thinking about the observation in an apparently public space. But putting that aside, first, I find that Larry has articulated the distinction that I was struggling for...he’s gone now...and perhaps overstated when I was focusing on psychosocial or invasive. I think when I think about the problems of health insurance and life insurance and employment discrimination, I think about the language of rights. And that rather than thinking about that in the context of minimal risk or non-minimal risk, I think about it in the context of rights and welfare. That something might be minimal risk in all of its other attributes and nonetheless have a significant potential for adversely affecting somebody’s right to get reasonable treatment from these third-party actors, like insurance companies or employers. And I think maybe Larry put his finger on a better way of trying to split this, and it certainly can be used to supplement the notion of minimal risk, or you can yank those out and separate them, whichever. I would like to understand better, though, within the concept of minimal risk, how people are understanding the part of the phrase that deals with probability of harm anticipated in the research, not greater in and of themselves. Because outside this whole thing about employment discrimination and such, are we doing kind of a gross mathematical average—what’s the probability that I’m going to be psychologically disturbed during the course of a day or a year compared to the likelihood of being disturbed by this experiment? I’m struggling, I’m truly struggling to figure out how to handle this. And last, just as an informational note that goes in the medical records stuff. You alluded, I think, to the fact that the research results are not recorded in the medical record. My

understanding is that at least at some hospitals, as a condition of certification, every lab test done in the hospital on somebody who's got a record there has to have the results recorded in that record, even if a lab test is done as part of a research protocol. And as a result, a number of protocols that we review we required this kind of notice to people that the results will be in their medical records, not in some special vault. And that that's within the control of the institution, that's in the control of the certification agency.

MR. HOLTZMAN: Just on that point, I think it's an area that's in tremendous dispute right now. There's legislation that's in various places saying it ought not be.

DR. SHAPIRO: Okay, I've got four people on the list, including you, Bernie, and then we're going to take a break. Eric.

DR. CASSELL: Well, step-by-step, Steve, I think you're right. The harmful thing is information, we're not talking about direct physical harm, we're talking about information harm. We're so blunted about the invasion of privacy in the current world that we forget that it has been considered a risk of harm, medically considered a risk of harm for at least 2500 years, and that's why it's in the Hippocratic Oath. And this potential for harm by information that reveals something about me, even that I have cancer if I don't want anybody else to know that, is enormous. It's a risk that I take when I go to a physician. There is a second part of it, of course, and that is that I give consent in the sense that I'm giving this directly and therefore participating in the sharing of information. So I'm...three points at least, I find no distinction. I think the concept of minimal risk does apply and can be overridden here in information terms. And it isn't merely physical and we ought to be very, very careful about it.

DR. MESLIN: Just very quickly. As staff was going through this discussion, we want to have Commissioners pay attention to at least two things, and I think they have paid attention to them and it's now a question of what you want to do. The first is in the definition of minimal risk, which Tom Murray has read out to you. There isn't more with respect to how one makes that assessment. The everyday life part or the routine care part. There is no requirement that IRBs adopt one or the other. This is just the definition of minimal risk under 46.102i. Having said that, which means you won't have to make the determination as to whether the risk that one is exposed to in this study is comparable to the risks of everyday life were you an IRB member, you may choose as a matter of your discretion and judgment to adopt the other referent, which is routine care. Having said that, and this is probably where Alta was going when she talked about where the sections of this chapter might best be illustrated, were you to leap forward to page 191—only two pages is not much of a leap, it's sort of a step—lines 15 to 20 and then on to the following pages, describe what IRBs with respect to the Federal regulations may do, should they, must do rather, should they wish to waive consent requirements. And those are listed as 46.116d, etc. And these are cumulative. These are not ors, they are ands. All four criteria must be met. If they are not, meaning if any one of those criteria are not met, and you, for purposes of argument here, select one, the research

involves no more than minimal risk to subjects, then it immediately kicks back the trigger to IRBs that they must think about consent. And if consent is required, then it becomes an issue of how one discloses the risk to subjects, what the consent form looks like, whether individuals may choose as a result of that disclosure to participate in research, knowing that there's a probability of a certain type of risk which they, the subject, can judge to be acceptable or not. This may have been where Alta was going, I don't mean to predict where you were going. But staff did struggle with where to put these sections—waiver of consent, minimal risk, rights and welfare—and I hope that in the course of the conversation that continues, you can both advise us what would be the most logical order of that presentation and not confuse the illogic of the order, so to speak, with the content.

MS. HANNA: I just want to add one thing. The reason rights and welfare—it's problematic as to where to put it—is because it is part of the calculus in determining whether you're going to waive consent. It is not part of the calculus when you're determining whether you're going to expedite review. And so you're right, if we flip them, then we would introduce the concept of rights and welfare first. Because rights and welfare can and should be considered even in expedited review, although it does not say that that's a condition that triggers expedited review.

DR. MIKE: Before we go on, Harold. It's just that on page 190 I get totally confused between minimal risk...the separation between minimal risk and rights and welfare. It looks as though they're put together.

DR. GREIDER: I just wanted to agree with the discussion we had that what we were discussing here as minimal risk is the information content. And I appreciate Alta's way of thinking about some of these issues, but just have to keep coming back to the fact that the term "minimal risk" does appear in chart Y and these other areas. And even if we're going to think about it in terms of rights and welfare, we need to somehow incorporate that language, because minimal risk is a yes/no box on this chart. So we have to somehow fit what we're going to say into that category to some degree. And then the other issue I wanted to do is to get back to the medical record discussion that we were having. I think that what Alex said relative to my first comment about the circularity of it was probably more clear as to what was bothering me about using medical records as an example. Tom disagrees with that view. He thinks that medical records are a reasonable example of the risks that you encounter in everyday life. But I think we all have to keep in mind that this is a moving target. That right now there's a lot of information going on, as Steve pointed out, or a lot of action going on in terms of medical records privacy. There's a lot of concern, there's legislation, et cetera. And for us to tie something that we're going to say to the medical records are of certain degree of risk, I feel like we're tying something to a moving target that already is very uncertain. And so that's an additional reason why I just don't feel that using the risk associated with your medical record being disclosed is an appropriate one as a criterion for minimal risk.

DR. SHAPIRO: Bernie?

DR. LO: I want to follow up and support Eric's comments calling our attention to what the policy implications of our analytic discussion of minimal risks. And the real question stated here for researchers and subjects is the informed consent issue. That if we don't think that research on human subjects involving DNA testing is minimal risk, then it automatically kicks in to the "get consent from subjects" category, which has a lot of implications for doing this kind of work. So we're forced to deal with this concept of minimal risk, at least that's the way the current regs lay it out.

I think we do have to—I mean, again, we're dealing both with sort of a philosophical clarification of policy implications, but somehow whatever we decide what minimal risk means, we then have to deal with the issue of do we think it's appropriate or inappropriate for research on stored tissue samples to be done without consent of subjects, subjects of the other three criteria?

I was particularly attracted to the notion of special consideration or special scrutiny, because I think one could plausibly argue that even if you think that a lot of research involving stored tissue samples and DNA testing is minimal risk, there are certain examples that we can all think of that probably aren't. And we need to make some distinction between the special cases and the more usual cases.

So I think that the more we can highlight the differences, the gradations that intuitively are there and concern people, I think the richer our discussion.

I want to make another point about minimal risk. We haven't talked very much about the protections that are built into the protocols. It seems to me that risk is not just a function of the probability and magnitude of harm occurring, it's the steps you take to mitigate or minimize those harms. And it seems to me one big difference between research and clinical medicine is that in clinical medicine there are a lot of protections that get built in in terms of risks that have to do with confidentiality. And I agree with Carol that a lot of it's up for grabs now.

I think the way research data is handled is very different than the way medical records data is handled, and only because you have a medical records department that really has as its sole job the collection, dissemination, and storage of medical data. But with researchers, I keep all them. Students who work with me, they keep their stuff piled on their desk and someone could just walk in and look at it. And I have to say no, no, you can't do that, you've got to keep it under lock and key; if you're going to code it and you've got to keep the code somewhere else.

It seems to me we need to somewhere say that even if we do decide that a lot of research on stored tissue samples has minimal risk, that's subject to the provision that appropriate standard of care for the protection of the confidentiality of information is

there. I don't think that's really in our report yet, and I think it's really important because a lot of investigators don't pay much attention to it.

DR. SHAPIRO: Tom and Steve, and then we're going to really break. I'm writing more names down.

MR. HOLTZMAN: When Alex began the discussion about whether medical records were inappropriate, sort of an analogy of the standard of care, Alex has made an argument which is quite correct. The conclusion of the argument was that therefore by these records we deem minimal risk, and in fact the risk of revealing information from medical records is more than a risk of everyday life, or that this risk of having records revealed from this biological research would be greater than that of somehow having it revealed from medical records, then that wouldn't be minimal risk. So this isn't just an academic discussion in a sense, it really is a very substantive discussion. I'm glad we're doing it.

Particularly what Carol and Bernie have recently said, I'm persuaded at this point, although I never underestimate the power of my fellow Commissioners to show me I'm wrong, but I'm persuaded at this point that, if anything, it heightens the need to stress the relative similarity between the medical records and the records generated in this kind of research. Yes, protections, we hope, will change and in fact become more stringent to medical records. To me, that is a good thing about stressing the similarity because then IRBs ought to be mindful of the protections afforded to medical records and they ought to insist that if you want to call this minimal risk research, then you better make sure that your records are protected at least as well as the medical records are protected, heightened by Bernie's comment about how sometimes they're not cared for very well and that's a problem. If, in fact, information gathered from the biological materials are left strewn around the lab and anybody can walk in and look at them and figure out who they belong to, that's a problem. And so I'd like to, if anything, heighten the analogy.

DR. SHAPIRO: We can have a break. Let's try to reassemble in ten minutes.

[Recess.]

DR. SHAPIRO: Colleagues, let's begin our meeting again. We're going to have to move on through this document although we have not resolved a series of issues here. Let me turn to Eric for a proposal as to how we take our next steps and then try to move on to some other aspects of this chapter.

DR. MESLIN: Very briefly, I think the break was helpful for some of the Commissioners who have been trying to put some ideas forward to come up with a proposal. I'm going to suggest or request that the Commission ask the staff to spend some time on pages 189, lines 7 to 13, describing two things. The first, the actual problem that the rights and welfare issue raises for IRBs who must make an assessment

of minimal risk. And secondly, to relate that discussion to the earlier discussion in this text about how minimal risk itself is a problematic concept, not so much in the regs alone but as applied to our report.

I think it is fair to propose that based on that kind of writing, the Commission can still retain its belief that the regulations with respect to minimal risk are adequate, which was our initial statement, adequate, but that further substantive direction would be useful for IRBs in this area. Staff, I think, is very able and willing to provide that material, with input from Bernie and Alex and others who have been offering comments on that.

I think that if we spend more time on this, we will spin our wheels. There has been enough conversation and we can go back to the transcripts. I don't want to offer this now, but it is possible, since there are laptops around the room, that before the end of the meeting tomorrow some initial suggestion can be provided to Commissioners so that they can at least offer their assent to that direction rather than having to wait for a new draft months hence. If that would be acceptable, then I'm sure we can oblige. We will try to write something and we will try and get it back to you before the end of this meeting which meets some of these concerns?

Professor Capron: I don't believe material in Chapter 4 or here adequately addresses what we already have in the transcripts. Early on there was a very good statement from Alta I thought that, as I recall it, had two parts. One was the problematic nature of the present definition for what it covers. The other is the particular difficulty of applying that definition to psychosocial harms which we recognize—as Larry reminds us today, the tissue doesn't feel pain—are the only kinds of harms that are really at issue here.

And for all the wandering around on the issue, and some examples about screening and so forth, I would like to see us take a much more direct approach here and say that the regulations as presently written don't do a very good job here. The concept which the present draft points out, that if there are risks in ordinary life that are much greater, that are "substantial" is the language used, that those still would qualify as minimal risks is, of course, incoherent.

The whole idea of this goes back as far as I know to a study done more than twenty years ago by people from the Research Office, I don't think it was even called OPRR at the time, and Bill Dommel I think was the lead author when it was published. That study looked at the then-existent findings about research studies and said, they don't seem to cause a lot of harm; indeed, researchers seem to be more careful than ordinary physicians. So all this stuff about being so concerned. And then they looked at some of the data on what are the risks of ordinary life to people physically and they said, gee, these don't seem to be greater. And from that came the concept that when you're below that level, when your research is just some ordinary kind of research, it is like going to the doctor and having an ordinary test.

The thing about routine physical or psychological exams is that they are done without real consent. You go in and you see the doctor and they take the urine and the blood, and they take your weight, they listen to your heart, and so forth. The doctor doesn't say, "By the way, when I'm done with this I might find out you have a deadly cardiac problem." You have the sense this is just a general checkup, it's routine, it doesn't involve much physical risk, and I don't really get much informed consent for it. It is only once the findings are going to be there do you really get a chance to say anything about it. That's the general sense. And most researchers are in that same category. That's the origin of this language.

If we're saying in fact in ordinary life now, because medical records are totally insecure, if you have a medical test, you are potentially wiped out in terms of getting health or life insurance. We would not consider that a minimal risk in any ordinary sense. And that's why they are such a bad example. It isn't the content, it's the fact that most people still probably have a sense that you aren't at risk because it's confidential; the doctor will keep your records confidential. You have to sign something every time they supposedly release it.

I just find the discussion just does not match our prior discussions. So when you tell me that you're going to come up with something that reflects our discussion in the transcripts, I'm not sure that it's going to get to what seems to me a year ago was already quite clear, which is this language isn't adequate on its own terms, it doesn't meet the particular problem that we're looking at, and we can't simply say that it's all fine and hunky-dory.

Now would you like to hear something I feel strongly about?

DR. MESLIN: Let me just give a quick response. If your proposal is that you think the reg's definition of minimal risk ought to be changed, that we, NBAC ought to make that as a recommendation, I didn't hear that in the discussion.

Professor Capron: No. My proposal is not that, because we've been told repeatedly that if we say the regulations are going to change we're just whistling in wind or something, whatever the phrase is, or a futile activity.

What my proposal would be is that Chapter 4, Chapter 5 shouldn't be a place where much discussion occurs, it's a place where we're supposed to come to conclusions. I would like Chapter 4 to say what kinds of problems you face with using that definition just as an IRB facing anything, and then why there are particular problems here. It does some of that, and it gives some examples, but it doesn't really come fully to grips with the notion that the language about "ordinarily encountered in daily life" or "ordinarily encountered during the performance of routine physical exams," what does that mean as it would be relevant to thinking about examining tissues and cultures and so forth, and to show just how inadequate it is in addressing that.

We could then do the following in this conclusion. We could say what we think should be the view, and then go on and say, if that is not consistent with the present regulations, then we believe the regulations need an interpretive gloss from OPRR and the Human Subjects Interagency Committee, or revision if they don't feel they can gloss it to the extent necessary.

We're dealing with regulations that were not written to address this subject. I do not in any case think we should spend a lot of time on the exegesis of the regulation themselves. We should come to the conclusions. There are more-than-minimal risks in studies that should not be called minimal, although very substantial, and thereby evade the whole notion, which we keep coming back to, which is those are situations in which we don't want expedited review and in which potentially you do want someone to be faced with the notion that this could be a study to which they should consent.

All those ideas swim around here but they don't come together.

DR. SHAPIRO: Well, it's my own view that the minimal risk as defined in the regs is not any kind of normal meaning of that term "minimal risk," which leads to all kinds of issues which you've highlighted here. And if what you're saying, Alex, is we need to really go at that directly. I agree with that because, as you pointed out, minimal risks can be very substantial given the way they are defined in the regulations. We do have to deal with that. And we circle back all the time because the word "minimal" keeps on fooling us.

Professor Capron: Let me emphasize, I think the origin of all of this, to the extent that it is connected to the Dommel study, was trying to make the point that people thought of research as very risky and that it really was the kind of thing that shouldn't bother you because it was just like everyday life. One thing since then we've learned is that a lot of research was carried on that was very risky and was disguised and hidden. But that wasn't on the table when Dommel looked at it.

Secondly, I think we recognize that the risk of ordinary life vis-a-vis things like private information being disclosed are much greater than he was looking at. Ergo, the term that is going to remain there ought not to override common sense. That when you get substantial risks they shouldn't be saying, "Well, it could happen in ordinary life." Ergo, waiver, exempt, expedite, or whatever.

DR. SHAPIRO: I agree with that.

A number of people. Bernie, then Diane, Steve.

DR. LO: I share Alex's concerns that in our reluctance to overturn the regulations because that wouldn't be very fruitful, we end up perpetuating uses of language that contradict the plain meaning of the terms.

It seems to me that what we're facing is similar to what judges must face when they have precedents they don't want to overturn because it would just be too messy but that they really in some sense disagree with. So I think what a lot of clever judges do is they say we uphold the previous decision, we agree with it, and then 99 percent of the decision is saying what's wrong with that decision and how what we're doing is really different. We may need to do some of the same chicanery. I just, however, want to make a plea. I just taught a big class yesterday to bright-eyed, eager, first-year research fellows on the ethics of research. They are going to be totally confused when they see the term "minimal risk" and then our discussion. I think the price we pay for upholding the precedent is that we perpetuate some fairly peculiar uses of the language that lead to a lot of confusion among young people. I think we're stuck, as I agree we can't rewrite the regs at this point, but I think we need to be very, very skillful at pointing out we're keeping the term and basically redefining it.

DR. SHAPIRO: Diane.

DR. SCOTT-JONES: I think it would be useful to get the study Alex mentioned, the Dommel study that led to minimal risk. I think it would be very useful for all of us to read that.

I would like to say that I very much agree with Alex and I think we do need to make some sort of statement about minimal risk. I agree that we shouldn't try to change regulations. And I've probably said this before more than once, but in our research with children there is a fairly widespread recognition that the standard "minimal risk" is one that's confusing and not that useful, and some researchers, Ross Thompson is one of them, have recommended that we substitute a standard of "decent treatment" for children for the notion of minimal risk.

DR. SHAPIRO: Steve.

MR. HOLTZMAN: I think Kathi mentioned earlier that I think it was OPRR 4-6 years ago issued an interpretive gloss in the context of genetic studies about minimal risk and that it should include psychosocial harms. Have we distributed to ourselves a copy of that?

DR. MESLIN: That was part of the OPRR Guidebook that we previously distributed to the Commissioners.

MR. HOLTZMAN: Right. So we have in hand what a gloss of minimal risk from OPRR looks like in the context of psychosocial. So it might be worthwhile for us to look at that again.

DR. SHAPIRO: Alta.

MS. CHARO: A few quick items. First, something we shouldn't miss that adds to the confusion here and it's very pertinent for this kind of research is the enduring

confusion, at least in my own IRB about whether the assessment of minimal risk, whatever that term means, is made with reference to the particular subjects you are going to be studying or with reference to the general population.

Sometimes the particular subjects you are going to be recruiting are people who live in unusually dangerous circumstances or they are people who are already very sick and are seeing doctors regularly for big-time, big-risk medicine. The question arises, does this research protocol which has a risk level of this, which would be more than minimal risk by anybody's understanding of it for the general population, nonetheless remain minimal for this particular subject population because they are already going through so much more? And it comes up, for example, in cancer studies where people are undergoing chemo, et cetera, et cetera.

This is pertinent here because I'm thinking about the Mary Claire King descriptions, in which she's looking at people who have already been extensively involved in the medical system, extensively tested for one genetic marker or another, and who are now being faced with the question of being tested for yet a different one, for whom the risk of things like psychological upset due to confusing, potentially alarming results about which you can do little, or the potential for discrimination or stigmatization has already existed by virtue of previous interactions.

If we're going to make a serious run at the problems with minimal risk, I think we probably want to make a serious run at this problem of knowing of whether it's with reference to the particular subjects or the general population, because I think that's going to happen here frequently.

Professor Capron: We have a presentation adopted by Gary Ellis about that.

MS. CHARO: If we did, then I've forgotten it, which happens frequently. I'm sorry, I can't hear what people are saying. Is there an answer to this question? If I just missed the answer, that would be great. I'd love to know there's an answer.

DR. SHAPIRO: I guess the issue to me, Alta, that is relevant but yet another example of the problems with the uses of the words "minimal risk."

MS. CHARO: I agree.

DR. SHAPIRO: There could be quite substantial risks, and I think the question you pose is an interesting one, whether we always refer to the population as a whole or whether it's relativized to the people that you're actually looking at in the sample.

MS. CHARO: All I'm saying is that if we're going to be doing a serious discussion of the problems with this standard, if there's an answer, let's get it, and I'd love to hear what it is. If there's no answer, let's identify the problem and we might even want to take a run at an answer.

Finally, on the question of how to handle this section which has been the discussion up until now, it may be that we're going to wind up having to say that most of these psychosocial risks either exceed our best understanding of minimal in magnitude, or that they adversely affect rights and welfare. One or the other, or both.

But that with regard to the minimal-risk portion of it, the safest thing that researchers can do is work not on the magnitude, work on the likelihood it is going to come about. There is a little bit of language in there now about focusing on efforts to ensure confidentiality and protect information backflow. That may be in the end the only real solution is to work on the likelihood of the harm coming about because we'll never be able to adequately characterize the harm as minimal or non-minimal intrinsically.

Professor Capron: Why not? Being hit by a tricycle and being hit by a truck are two different things. Despite the fact that I have equal probability of them doesn't mean that they are equal. I don't get it.

MS. CHARO: I thought that we were agreeing that we're having difficulty in identifying what constitutes a risk that is or is not similar qualitatively to the risks of daily life.

Professor Capron: The probability and magnitude. They used the term "risk" very sensibly.

MS. CHARO: I understand. I'm saying that the focus on probability may be more fruitful because the focus on the quality of the risk may get into these endless moving discussions that don't have good answers. If you minimize the possibility of the truck accidents sufficiently, you are allowed to not characterize the overall risk as greater than minimal. And this may be a more fruitful way to design your protocol is to focus on minimizing the probability of harm.

Professor Capron: Well, as to any one protocol, the magnitude may be a given, if that's what you're saying, and you want to minimize the probability that it will happen. But as between protocols, one could be minimal although it involves a substantial likelihood of something happening. I mean, the fact that I will get pricked by a needle to draw a sample is 100 percent in certain situations. But a prick to get a drop of blood from my finger—

MS. CHARO: I'm not talking about blood pricks. I'm talking about the possibility that you're going to wind up losing your life insurance. We can't say if losing life insurance is greater or lesser than daily life because you can lose your life insurance in daily life. But if we minimize the probability sufficiently, we can still meet the minimal risk standard. That's all I'm saying is that it may be more fruitful to focus on probability.

DR. SHAPIRO: I understand Alta simply to be saying that research designs, whatever the harms are, should be designed to minimize risks given whatever the harm is.

Professor Capron: No. I understood Alta to say that probability is what the IRB and the investigator should focus on.

DR. SHAPIRO: In any case, we're going to have to move on here. First, Alta, in response to your question, I had really meant to respond directly to it. You were wondering whether it's the general population. My understanding of what occurred is it's the general population, whoever that is and however that is. Now Gary can tell us if that's wrong, but that's what I recall. So whatever that means and however you feel about that.

All right, Gary, tell us. Was I right or wrong, Gary?

DR. ELLIS: You were correct, Mr. Chairman.

Professor Capron: Isn't that in materials that are available to IRBs?

DR. ELLIS: It would be available on transcript of the NBAC meeting when I addressed it. Alex's memory is correct. Remember, we had a long discussion and I posed a teaser whether lumbar puncture was greater or less than minimal risk. It's possible that Alta was not at that meeting.

But Chairman Shapiro is correct. Just to be brief, we know it is not the daily life of a healthy person because the department specifically turned away from that language in 1981. We know it really can't be the life of a person who is very vulnerable because then we would be inflicting more harm or discomfort on the most vulnerable person and we go down a slippery slope. So we're left with the conclusion that it must be the daily life of the general population, which includes people who are of ill health. I don't know how better to explain it.

DR. SHAPIRO: Okay. Thank you very much, Gary. I appreciate that.

Tom has a comment, then we're going to move on to the issue of practicality.

DR. MURRAY: I hope this comment can serve as part of the segue. The discussion has been helpful in clarifying some things. Alex had called for sort of a beefing up of the discussion of the problems with minimal risk in Chapter 4, is that correct? Do we all agree with that? I think that's right. I think we should say that, be very blunt about it. Then we still have to make a decision in Chapter 5 about how to cope with it.

I hope I read this correctly, but as I understand it, with all the problems, if we were to follow the interpretation, the definition of minimal risk, what happens is suppose you say, well it appears to be not greater than minimal risk, that kicks us into Chart Z, doesn't it? Is that right? Where the first entries were the research in its entirety involve greater than minimal risk. If the answer is no to that question, and sometimes we're going to think it sort of defies common sense to answer no to that question because we think the absolute risk is high, you get a second bite of the apple. Here's how you get it. You go two steps down and it says, if it's not greater than minimal risk, it's not practical

to conduct the research without the waiver, then it asks, will waiving or altering informed consent adversely affect subject's rights or welfare? And you can say right, it does. It puts them at risk of losing their insurance. There you get to look at the absolute level of risk and say yes, it would adversely affect and therefore you can't waive consent.

So I mean, in a set way, common sense gets a second hearing. And so if I understand the way it would proceed, I'm not uncomfortable with saying, this is a tolerable way of handling it, even though at the first cut—when you say is it minimal risk or not—it's not the common meaning of the term. You do get to revisit it later on, if I understand it correctly. And so as a practical matter, you do get to introduce his concerns about the absolute level of risk.

DR. SHAPIRO: Okay. Thank you very much.

There are, between where we had begun looking and the practicality section, which begins on page 194 with a call for recommendations two pages later, there are, of course, some comments on consent and on the rights and welfare issue. I think Alta had a very helpful, I thought, editorial comment before. That's my own view of that. We may want to come back to some of that later.

But let's go directly to the so-called practicality section. It begins on 194, then it has a bold-type conclusion, I guess, at the bottom of page 196, and then, I don't know how to phrase this, Kathi, but a suggestion or something that you want us to think about or talk about.

So let's see what comments and reactions there are to that bold-faced conclusion, and the material that Kathi has been involved with about that.

Alta?

MS. CHARO: Page 196, lines 6 and 7. A clarification. Where it says "it's important to remember that reasonableness has to be reviewed in light of the level of risk of a study that is above or below minimal risk," I think it's important to keep in mind that this issue or practicability is only coming up in the context of the waiver of consent, which is only permitted when you have research that is minimal risk. So that the level of risk that you're worried about here cannot be above minimal risk or you're no longer even worried about practicability. If it's above minimal risk, you're not allowed to waive the consent anyway. So just as a clarification, I find it increasingly difficult to keep all these rules in my head at the same time.

I would like to just ask for the purpose of trying to flesh out the discussion here, which is struggling because we're struggling, whether we would like to start from one threshold question, whether people should be required to at least try to obtain funding sufficient to permit contact, and only when that funding is not going to be available be able to make the argument that it is uneconomical and therefore impracticable to get consent.

It has an effect on the way in which people write their grant applications. It kicks some of this question back up to the funding agencies about their priorities in terms of funding numbers of protocols versus funding fewer protocols and greater protection. And it begins to get a handle on the economic question.

DR. HANNA: I actually talked about that possibility with some people who are grants officers at the NIH. They expressed a concern that it might initiate a trend by study sections to deny funds for that use and therefore give the ammunition to the investigator to go back to the IRB and say I tried and I couldn't get it funded, therefore it is impracticable. So that's just their side of it.

DR. SHAPIRO: Carol?

DR. GREIDER: Another response to that, that was a very creative answer about the grant funding, but just in terms of practical issues, the turnaround time for applying for and getting a grant is a year, year-and-a-half. So that would definitely change the ability to at least initiate something. People should be aware of that, that it is not a simple thing of just applying and being denied. That would be a delay of a year-and-a-half.

DR. SHAPIRO: Other comments or questions with the issue of practicability and what we might want to say about this?

Steve?

MR. HOLTZMAN: It's a question and I think Alta pointed at it in those specific lines. Do we read practicability as a standalone condition, or is the reasonableness modified by something else? I think what Alta's just pointed out that the way it was written, your sentence reads, "the reasonableness of the contact effort has to be viewed in the light of the levels of risk." Alta rightly says that's not in play anymore.

My reading of it is practicable sort of stands alone. Practicability is not a function of whether or not it is worth doing for other reasons. You seem to want to modify it. What is our reading of this? What is the interpretation that's out there right now?

MS. CHARO: This is a very imprecise answer, right. We're completely within the realm of things that are minimal risk, whatever that means. The kind of gut reading of this thing is, of course, you're supposed to still go out and get permission from people unless you can show that it's really not going to make any sense to try, and here are the reasons why it's not going to make any sense. And that's what we're trying to fill in.

Now I agree with you that the not making sense could be that the cost exceeds the cost of the entire protocol or some substantial portion thereof. But I do feel like somewhere buried in there is also the degree to which people would care that they were never contacted. I do think that there is still some role for this, not so much level of risk as much as perhaps expectations of privacy, personal autonomy and dignity on the part of the people who are suddenly not going to be asked somehow is a factor and looking

at the amount of money that one ought to spend to recontact. I think there is still a mix there, although it may not be risk.

DR. SHAPIRO: Alex?

Professor Capron: I agree with Alta. The notion of reasonableness can mean reasonable under the circumstances. And sort of the interest you have in not having something found out about you or a group of which you're a member or whatever comes in there as well as in the additional requirement of the other conditions; namely, Tom reminded us that you still have to have a rights and welfare barrier before you waive consent. And if what's being found out is not anything that's likely to be very upsetting to most people, et cetera, et cetera, it comes in there.

Reasonableness, we can comment what reasonableness takes into account what you're saying. If you're finding out whether or not a person carries a very deadly illness, the effort you would make to get hold of them first and ask if they are willing to have a study done, you can grade them to be reasonable then if it's a trivial matter.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: When I read the regulation I don't see the word "reasonable" anywhere in there with respect to this. And I think what's psychologically taking place is because we've read "identifiable" as "possibly identifiable," because we're reading "minimal risk" as "any risk." We're looking for escape valves but I don't think "practicable" is the place you should be finding the escape valve.

DR. SHAPIRO: Eric.

DR. MESLIN: Just a couple of quick comments. We have heard case examples of studies for which the re-contact effort or the consenting effort would be difficult either because of feasibility issues (it would involve a great number of people, a great amount of money, or might take longer to do that than the study was designed for in the first place). Those are study design issues which are what staff has described on page 197 in the italicized box, which is the "Cliff Notes" version of things we would like you to think through, lines 1 to 7 on page 197.

The other portion of that practicability is the cost issue. At our previous meeting in Portland, we tried to spend a bit of time talking about whether cost alone should be seen to be a ground for declaring consenting to be impracticable. I just hope that as you go through you consider the following options: (a) do nothing because the regs, as we've seen from our personal communication with OPRR, do not provide us with a criterion for defining practicability, which kicks it into the discretion of the IRB to determine on a case-by-case basis; (b) the option is to focus only on research design issues where practicability is the equivalent of feasibility; or (c) practicability being simply seen to be a financial barrier which either for budget reasons in a grant or other reasons, just the volume of dollars that it would take would be seen as a bar.

So I think what we're saying in the draft is there are a number of options you have. Option A is to do nothing and suggests that IRBs think about this very carefully and provide some explanatory language for what makes it difficult; or B, to make this distinction between financial practicability and design feasibility. That's, I think, the direct that we were trying to suggest you deliberate.

DR. SHAPIRO: Alex?

Professor Capron: I guess I want to first disagree with Steve. The word "practicable" here is not the word "impossible." It seems to me that our use of the word "reasonable" is more in line with what's involved in interpreting what's practicable than you suggest. You said it is a bad place to put our interpretation to allow a study that has made a reasonable effort to go forward because it doesn't say "reasonable" it says "practicable." I would look at it the other way and say it doesn't say "impossible."

MR. HOLTZMAN: Can I just quickly respond to that. I think the kinds of considerations that Eric was pointing to in terms of practicability, in terms of it's in the nature of the study that you can't recontact those who were in the study, all of that correctly builds in. My argument about practicable was not trying to build into that concepts of it is reasonable given that it is minimal risk or given that it is the cost versus the potential harm. I think those kinds of considerations play themselves out elsewhere in the regulation. Whereas, if you look at our language here in this part of the section, what counts is that for reasonable effort to be made clear, self-compliance, you know, specifically when we're looking at things like the potential adverse impact of the rights and the welfare of the subject. And I don't think that does play into practicable. That's my point.

Professor Capron: I guess I disagree. If I could continue the comment. I do agree that there is a design issue where you can say it's not practical because you will end up with results that don't mean anything if we design this way or that. I disagree, however, about the inclusion of the material from lines 3 to 5. And maybe you could explain that to me and I would be convinced. On page 197, the argument that the research is so valuable that it ought to be conducted even though an effort could be made and so forth, I find is a totally different kind of argument. It is a collective interest which individual research and IRB ought not to be able to exercise. And if anything, it would seem to me that the argument would be if you're really getting something of such extraordinary benefit, you ought to be willing to pay the extra design. Because on the other side, as suggested in that exchange, although I think Carol is right and it is kind of burdensome to say go and submit your research, put in the extra \$100,000 to hire a private detective to trace all these people down, to be told that that's a ridiculous part of the budget, we won't fund it, and then come back to the IRB. But it's more a matter of common sense that a person says look what I'm doing, clearly I'm not imposing a huge risk on people, these are 10-year-old records, the chance if I try to find these people is very small given what information I have that I'll reach most of them, I'll ruin the research design because

I'll have this random factor that's introduced and I don't know the meaning of it, it would cost \$100,000 to track them all down, it's a \$50,000 project, it isn't practical to do this." A person could say all those things and not be misusing the English language, and an IRB hearing all those things could say, yes, I agree, that criterion of impractical is being met here by those considerations.

DR. SHAPIRO: Tom?

DR. MURRAY: Partly I'm going to try to restate. People will tell me whether you think I've got it right. As I read the language, which is research could not be practically carried out without waiver or alteration, it seems to me that some sort of proportionality judgment is being called for. It is not some absolute standard of practicality, is just some fiscal impossibility, or is more money than the world has. That can't be the standard. Some kind of proportionality.

If I understood you correctly, Alex, certain factors can figure into that judgment, like how big, what can figure and what can't. One thing that I think cannot be figured in is, well the study is really important. That's not a practicability consideration. I don't think Steve and Alex disagree on that. Okay. So it is proportionality. We understand it to be a kind of proportionality judgment from which certain things are excluded from consideration.

Professor Capron: Proportionality of the risks to the individuals involved and cost of allowing them to consent? Not just dollars, but cost to the value of the research and all the other burdens.

DR. MURRAY: Because in fact one of the things that in my view affects practicability, among the costs of that you factor in, is maybe the subjects wouldn't want to be bothered about it, wouldn't want to be reminded. But it could be intrusive. I think we need to count that. You're right, we need to guard against it becoming kind of an excuse in terms of being an excuse to not talk to people you don't want to. But we need to consider their interests and all the interests are not necessarily in favor of being contacted.

DR. SHAPIRO: Alta?

MS. CHARO: Looking on my own experience on IRBs and on this conversation, I have a feeling that what's actually happening in the world is that these four factors, these four criteria, which each in theory in the regulations have to be independently met, are actually being considered in kind of a gemisch. And that it might be that our best contribution here would be to emphasize the following points in terms of implementation of this language. That first, there is a presumption that consent has to be obtained for all research, minimal-risk or otherwise, and that it is up to the investigator to prove to the IRB's satisfaction that there are sufficient bases for either waiving or altering the nature of that consent. And second, that the investigator needs to prove each one of these

separately and explain for each one separately why that criterion has been met. That might focus the IRB's attention a little bit, too, so the discussions don't get mixed up, in which practicality and risk begin to get mixed together and one loses the separateness of the issues. Third, that we take advantage of the fact that the IRBs are constructed to have a committee that is made up of peers as well as public members reviewing this. Because when it comes to this last element of practicability, I think it is probably fair to make a list of things and the peers are in a good position to make some judgment calls.

One, is the cost of contact for the purpose of getting consent going to be high enough to prevent the study from occurring? Peers are in a position to understand the issues surrounding grantors, et cetera. Now the answer to that might be, yes, we'll never get the money for a full recontact. Does that mean that necessarily consent can be waived or altered? No, because we've already independently had to determine that the rights and welfare are not being adversely affected. So if the study is really not a good study to do without consent, it doesn't matter that the granting agency won't give the money. That's not going to be an excuse to go ahead do it without consent because we've already given grounds to require the consent.

Second, the design issues. Third, and here I think maybe we probably need to go a little farther, is the response rate going to be so low if you require consent that it will undermine the statistical validity of the study? Diane had quite a strenuous critique of Mary Claire King's point in Portland about that and it may be that in some studies there really will be a sample bias caused by nonresponse and in others there won't. Again, it's up to the PI to prove that there will be a sample bias caused by nonresponse that would undermine the value of the study.

I think it is also, finally, something that we should maybe emphasize, which is that the section talks not only about waiving consent, but also altering the consent requirements. This is perhaps a place where we might want to take advantage of the discussion about opt-out versus opt-in consent that takes place later.

It may be that you could make the case that opt-in consent is going to create a sample bias from nonresponse or that it is going to be extremely expensive because it requires multiple contacts to generate the final consent. But that's not sufficient necessarily to waive consent entirely. A simple one-time mail-out with an opt-out option as kind of a notice of opt-out. That's an alteration of the requirements for consent. Remember, it is still minimal risk, it is not adversely affecting welfare. This may be enough to bring the money down.

But this may be our best contribution: the emphasis on the presumption of consent, the need to prove each element separately, and just a list of these factors that the IRB can take into consideration as peers review these special pleadings.

DR. SHAPIRO: Carol?

DR. GREIDER: Just one comment that I agree with your dividing this up into four very carefully. And I think that this chart does that. I think about it very differently looking at that chart than I did reading it here. It looked like four things in a gemisch—

MS. CHARO: You like that word, huh?

DR. GREIDER: It's actually a German word so I know how to spell it. But this chart, I think, helps. It goes a long way toward doing exactly what you want, which is to divide these up and have people think about them separately.

DR. SHAPIRO: Alex?

Professor Capron: In passing, Alta gave an example vis-a-vis the design issue. I'm not sure I heard her correctly. What I would find an acceptable issue to highlight under the design is the bias that comes if you can only reach certain subjects. If you insist upon going to them. You were sort of saying you go to people and some of them agree to do the study and some of them don't, that bias. That argument, if it were an argument made on research design, would eliminate consent entirely.

MS. CHARO: I disagree that it would eliminate consent entirely because you would still have to determine it's minimal risk, you would still have to determine that it does not adversely affect rights and welfare. So it would not eliminate consent completely.

Professor Capron: But the basic argument that the fact some people agree to these studies and some people don't is a reason on a research design basis for saying that we should get rid of consent, whatever category of research for that matter. It is an argument that could be generalized, but, clearly, is contradicted by the whole presumption, which you correctly stated, the regulations start off with, which is that ordinarily people ought to be asked to consent, even if this introduces a bias to the research, that some people were unwilling to consent may be more group A or group B in your outcome and you bias things. Sometimes we have to live with it is what I'm saying.

The issue here is a re-contact study, if it ended up biasing because you could only reach a subgroup and you didn't know that were different, that bias is different it seems to me. And as you say, the researchers would have to argue why the difficulty and the chance variation would be enough to make them say people aren't going to believe my result if you insist upon this criterion.

DR. SHAPIRO: Eric, then Diane.

DR. MESLIN: Just very quickly, and this is a function of us going through Chapter 5 first rather than Chapters 1 to 4. We do give an example of the NHANES-3 study earlier on page 80 and have heard testimony from Dr. Speers at previous meetings on this. So while you read through that section, you may wish to revisit pages 79 to 80.

We're aware and have had communication from the CDC that as they design NHANES-4 they are going to be thinking about just precisely these issues. So I encourage you to remember that case study because it was one that was considered very carefully by the CDC for recontacting the twenty-odd thousand individuals who participated in that.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I just wanted to say again what Alex said, and that is that the research design issue may exist for all studies that you are going to allow that research should be voluntary. We always have the problem that not every person is going to be in the study. You therefore would have to show some systematic bias created by your contacting people by telephone and some people don't have phones. You would have to show some category of bias and not just that a person's right to consent means that you then have a voluntary sample and it's not the whole population.

DR. SHAPIRO: We're going to break in a few moments. But I tried to listen carefully to this discussion and I think the statement at the bottom of page 196, lines 17 to 19, without worrying right this minute about its particular wording, it reflects something I think the Commission supports; namely, other conditions are satisfied. That it is still possible to go ahead if an IRB is convinced that appropriate efforts have been made. And then it's a question of filling that out in some way by giving some examples and giving some flavor of our thinking of the kinds of things that might be considered as opposed to making another recommendation. As I understand, that's where this conversation has led, and I think that's the way we ought to proceed.

Professor Capron: In a way, Carol, I think it is somewhat separate because maybe, I've tried to rewrite this sentence, or maybe I misunderstood it, but this seems to be describing a situation in which initially the researcher said, I will try to get consent and then came back to the IRB and said I've tried, it hasn't succeeded, I think I meet the other criteria, please allow the study to go forward without consent. Is that correct? Now it is actually a separate issue to say what about the researcher who wants to say I want a waiver of consent, I don't want to go through this effort, I don't have the money or whatever to go through this effort, and here are the reasons I should be allowed not to go through it. And most, it seems to me, of our discussion here. So, in a way they are related but they are conceptually somewhat different.

DR. HANNA: So you're proposing that there should be two?

Professor Capron: I'm proposing that there should be two statements, and that in effect what we've done is gloss the word "practical." We've explained the kinds of factors that an IRB could.... And then, as Alta said, we've reminded the IRB that that is only one of the four questions they need to ask to reach a conclusion that they may alter or waive consent. Is that correct what we've done?

DR. SHAPIRO: Okay. Anything else on this issue? If not, then I suggest that we break and reassemble approximately 1:00. We have two hours left on our agenda, if I remember correctly, to go through other aspects of this. I hope we can get most of the way through this chapter so we can give the staff appropriate ideas about what our next steps should be.

So let's break for about an hour.

[Recess.]

DR. SHAPIRO: I'm going to turn the microphone over to Eric in a moment, but I just want us to get under way. I'm going to try to run this session, if necessary, as late as 3:15 if we need that time. Beyond that I don't think we can go—we have another subject we have to pick up this afternoon. We have a guest coming who will make a presentation and it would be inappropriate to go much later than that.

I also want to remind Commissioners, as we do often, that it's very difficult for people in the audience to hear if we don't lean pretty close to our microphones. So, while it's often inconvenient and awkward, depending where our microphones are and so on, please do your best to remember that for the benefit of those who are in the audience.

We have two sections in front of us now following all that we dealt with this morning—one dealing with the so-called opt-out provision, and then a series of important issues to be summarized into recommendations regarding the use of existing samples which are, I think, really quite important to look at carefully. So, let me turn the microphone, now, over to Eric to take us through those two sections.

DR. MESLIN: Actually, I'm going to pass it right over to Kathi. It's easiest to get right into this and let her describe what some of the italicized text on 199 and what follows. Kathi...

DR. HANNA: Right. The discussion about "opt-out"—it's been kind of bandied about at previous meetings, and in Portland it was discussed a little bit more specifically. But in trying to figure out where it fit within the regulatory structure, in staff discussions and in some discussions I had with Bernie via e-mail, I was trying to get a sense of where we would put "opt-out," because it doesn't really go into the consent category, and how it might be considered. So, the way it's presented here—we're presenting this, suggesting that it be considered as an extra measure of protection that an IRB might suggest or an investigator might undertake in cases where opt-in is either not required or necessary; where, in fact, consent can be waived; but where the investigator feels that—or the IRB feels that there might be sufficient reason—maybe it's because of special scrutiny cases—to contact research subjects, let them know that their samples might be used in this way and give them the opportunity to opt out. It's not a surrogate for consent in any way; it's just an extra measure of protection. So, that is how we

presented it there and we're interested in hearing what you have to say about that. So, why don't we just stop on the opt-out for now.

DR. SHAPIRO: Thank you, Kathi. It's an extra measure of protection. I think the way it's written it's an extra but optional measure, so it's another tool to give IRBs a way to help. Alta?

MS. CHARO: Okay. First, on the issue of the organization and where it fits in whole analysis, I want to remind us that the previous discussion in which we looked at the four criteria—minimal risk, etc.—that's with regard to waiving or altering the consent requirements. So, the discussions at opt-out actually fit very nicely in there because it's a form of altering the consent requirement. A PI that has persuaded the IRB that he or she has met the four criteria—minimal risk, practicable, no effect, no adverse effect—can be given by the IRB either no leeway—you've got to go for full consent anyway—or can be told, "Yes, we're going to let you do 'opt-out,'" or can be told that it'll be waived entirely. So, this fits in under the concept of alteration.

It also fits in, however, in a second sense—and this is, I think, what you're talking about with the additional protections in which—not that consent could be waived or altered, but in situations where there is no need for any kind of IRB review if you're talking about trying to create a category of things in which people apparently are not obligated to present to the IRB, are presenting themselves for IRB consultation nonetheless. And this is your special scrutiny kind of categories, and we'll have to talk later about how to operationalize that. Then this might be one of the many things the IRB could recommend to such a PI, along with study design alteration, consultation of community leaders, etc. But I think that we need to be very careful about separating out the two ways in which opt-out arises, and clearly the second one is in context where the person is not ordinarily going before the IRB at all at this point. It's not that consent could have been waived, it's that they didn't need to be in front of the IRB.

DR. SHAPIRO: Thank you. Bernie....

DR. LO: When you presented orally, you made an addition to the text that I thought was very important. You said the investigator *or* the IRB may have the option. I would suggest we include that language wherever possible so it doesn't sound like the IRB is running after nasty investigators saying do this/do this, but that in many cases a thoughtful investigator would welcome the chance to have a wider range of options for herself.

DR. CASSELL: Put this in the simplest terms. This means that there is a group of people from whom we do not have to get consent but they can say no, and that means that you don't have to go through the clumsy business of going and finding each one of them, but I can't say no if you haven't somehow gotten in touch with them. So, you have to find out who they are, and you have to send them some kind of—but you don't have to go and meet them and have them sign. Is that the intent of it?

DR. HANNA: Right. We were trying to separate out the various reasons why we might recontact an individual. One would be to have them opt in. One would be just to inform them that the research was being done, not asking for them to respond in any way. One would be to allow them to say that they did not want their sample used for that particular protocol and to opt out for that study or any future studies. And, then, the fourth would be to communicate research results to them that might be clinically significant and meaningful. So, you're right. In all of these cases you have to know who the people are and be able to find them.

DR. CASSELL: It's like "Take me off your mailing list."

DR. HANNA: Right. Right.

DR. SHAPIRO: Rhetaugh....

DR. DUMAS: There's a thin line between opting in and opting out. If the person does not opt in, have they automatically opted out? If they opt out they're not in.

Professor Capron: Right.

DR. DUMAS: But if they decide they don't want to opt in—

Professor Capron: If you have an opt-in, the usual consent requirement is an opt-in requirement.

DR. DUMAS: Yes. And if they don't consent—

Professor Capron: Then they're not in. If you had an opt-out requirement and they don't say anything, then they're in.

DR. DUMAS: Okay.

DR. SHAPIRO: Diane, Bernie....

DR. SCOTT-JONES: When this process is used with research on children, it's called passive consent, and what happens is that a letter is sent home to the parents of the child and it says "Return this letter if you *don't* want your child to participate," and it's often used in a somewhat deceptive way because that language is usually at the bottom and fairly small—so a parent not reading the letter carefully, who throws it away, has in effect consented to the child being in a study. And I think that unless you write this very carefully, it seems just like that—the so-called passive consent, where you send out a notice and the person has to contact you to say that you don't want to be in the study; otherwise you consider them in the study. And it's not very much of a protection at all.

DR. HANNA: I think that maybe it's not worded clearly. But I think that the way the text is written right now, "opt out" is only an option where consent has already been waived. Or could have been waived.

DR. SHAPIRO: Bernie's next.

DR. LO: Maybe it might be helpful for us to recall Mary Claire King's comments in Portland on this issue, where she said that there are studies where you have a whole population that you'd like to study and you'd like to give people the option to say "I don't want to be in your study." And what happens, not uncommonly, is you mail out well-written, meaningful descriptions of the study and say, "You know, we will use your sample unless we hear back from you saying you don't want to, in which case we'll respect your refusal." And she said what typically happens is a lot of people get the letter and say, "Oh, I don't care. Let them go ahead and use it." But you have the opt-in alternative, where they had to get back to you and say "Yes, it's okay to use me," a lot of people who in fact don't object to a study—which, you know, has had to meet all kinds of requirements for a level of risk and stuff to get the waiver for consent—a lot of people wouldn't mail it back, but it wouldn't be because they didn't want to be in the study; it's just that they didn't want to take the trouble. So I think it is important we make it very clear the difference between the situation Diane was talking about, where it really is a surrogate for consent. We're saying that the protocol is such that the IRB approved it with a waiver consent but the investigator of the IRB is saying, "We want you to go beyond that and give people a real chance to opt out by contacting them and giving them an option to say 'No, thank you.'"

DR. SHAPIRO: Alta?

MS. CHARO: I would understand this to be usable in the following situations: (1) where consent is—not where it's been waived, where it *could* be waived, because the four criteria for the waiver has been met, but instead of choosing to actually waive the consent, we're choosing instead to do something a little less easy on the PI and simply alter the consent requirement and use an opt-out. That's one. And, the second would be where consent was previously obtained, where the change in the nature of the research does not rise to the level where new consent must be obtained but where there's some feeling of discomfort at doing this without giving people some chance to pull their stuff out. That kinds of grays out where it's just below the threshold of meeting genuinely new consent. Am I correct when I'm saying those are the two circumstances we're talking about here?

Professor Capron: How's the second one different?

MS. CHARO: Because in the first, there may never have been any consent of any sort obtained for this research, and we're determining that it meets the criteria of minimal risk, no effect—no adverse effect on rights and welfare, etc., and that therefore this research can go forward without any consent. For example, I have tissue removed at a biopsy in which the only thing I was asked was, "Are you willing to have a biopsy?" And then that tissue was stored. There was never any consent that had anything to do with future uses of this tissue, right? And the IRB now gets a request for a protocol that's

going to study this and they determine that while it meets all the criteria for waiving consent completely, but rather than do that we're going to ask for an opt-out. So it's more stringent than what they could already be doing. That's the situation, the second one is where they recontact because there is an underlying consent; it meets adequately the standards of adequacy for further work with that tissue. But for whatever reason, the IRB would like to go...

DR. SHAPIRO: It's an additional step.

MS. CHARO: Right. And that—therefore, Diane, I think that the concern you have is maybe not—it needs to be placed in a context. They're getting a letter that they don't—that they don't have any “right” to get at all.

DR. SHAPIRO: Okay, Tom, then Alex.

DR. MURRAY: I really like Bernie's example. Anyone who wishes further proof that the principle—empirical principle that you've articulated, all you have to do is cite the Book-of-the-Month Club and any of those other places that rely on sending you stuff that you have to mail back. And, how many of us have gotten books we didn't really want because we somehow or other failed to mail them back?

DR. MIKE: Well, you can keep it.

DR. MURRAY: You keep the book, and pay for it. That's the problem. Nonetheless, I think this notion of an opt-out letter is a good one. Clearly, people could do one somewhat deceptively and abusively, as Diane described, but presumably IRBs ought to be on top of that. We want to see the letter you're going to send out. And I think—let's add that additional level of protection so that if someone felt strongly enough about it, objected strongly enough, they would at least at this point be given an opportunity to say “I don't want to be a part of it. I don't want my tissue to be a part of the studies.” I want to commend the staff. I think it's a good innovation and sensible.

DR. SHAPIRO: Diane....

DR. SCOTT-JONES: Tom's example of the Book-of-the-Month Club is an interesting one because in a court case, that phrase was used where the so-called opt-out or passive consent. It was referred to as a “book-of-the-month-club procedure,” because if you don't send it back, you are in the study. So the burden is inappropriately placed. But I suppose in the context that Alta has explained, it's not exactly that you've waived consent; you're somewhere in between the waiver of consent and actual consent. So, it just seems sort of like double talk to say that you waived the consent when, in fact, you haven't. You're using this sort of variation in actually getting consent.

Professor Capron: I was going to agree with you, Diane, until your last comment. It seems to me that Kathi's original description of the situation is important. This is a situation in which the first step that the IRBs should reach is that there is no requirement

of consent. For precisely the reason that you describe, the opt-out procedure is not the equivalent of consent. It is, rather, because of the concerns about special sensitivity, a sense that, well, we don't have to get consent but there might be a few people who, when they get this notice, will tell us, for whatever reasons they may have a special sensitivity about this, that they don't want to be included. And it would be better that we give them this opportunity even though we don't have to because we've met all the criteria, and not treat this at all—as you were saying in your last comment—as a form of consent. It *isn't* a form of consent. It is an opportunity to object, but it is not consent. How, for example, would this be used with the “addressee-unknown” response? In other words, if you were asking for consent and you got “addressee unknown, return to sender,” you're back with saying, “We got to find some way of finding this person.” I assume that here you say—well, that person isn't actually ever going to know about their opportunity to object because we don't know where to reach them, and we're not under any requirement even of finding some other practical way of doing that. Is that right?

DR. HANNA: Right. I think in the first case where consent—the waiver of consent was not granted, where the IRB said you have to get consent, and you can't find the person—well, then you can't use that. But in the second case, where the IRB's already said, you don't have to get consent, then either the IRB or the investigator decides that they just feel better if they gave the option to opt out and they didn't get a response. They could still use the sample, because the requirement for consent was already waived.

Professor Capron: You might want to say something like that explicitly.

DR. SHAPIRO: I have Steve, Eric, Larry, Diane—I hope then we can move on to the next part of this.

MR. HOLTZMAN: I think what we're all agreeing is the IRB has concluded that it has met the criteria necessary to be eligible for a waiver of consent. The key issue is then say.... Alta's formulation that this be an alteration of the form of consent, and I'm taking Alex to say in order to make clear that this is not consent in any meaningful sense of consent, we ought not say that. I think that's the argument, right? And that, we should say consent has been waived, right? Now, for myself—because I don't know if anyone else finds this useful—I have struggled for a long time with the notion of harms vs. wrongs. And I have really understood that the welfare and rights is much more real to me in terms of harms than wrongs. And the one of the ways I understand the opt-out is when it is in the nature of the study that there is no harm, but there's a potential for wrong because there is this sense that even if I don't view my cuticle as myself in hearing in it I may not want it to be part of certain kinds of studies. Oh, I see this as where that can potentially get addressed. Is that just me? I don't know if anyone else wants to go down that path.

DR. CASSELL: You are either contacting the subjects or you're not. The fact that the addressee is unknown and you can say, "Ho-ho, we're relieved now; we don't have to worry about it," then don't call it ethics; call it etiquette. It's polite to ask if they would like to opt out, but, you know, politeness only goes so far, whereas ethics is supposed to go a little further, so politeness rules should be followed....

Professor Capron: This is not virtue ethics.

DR. CASSELL: It's virtue ethics.

DR. MURRAY: Superarrogation—remember that word, Eric.

DR. CASSELL: Superarrogation. Well, okay. I just want to know in what category it fits. Now I know it's not etiquette; it's virtue ethics. I want to ask Ed Pellegrino about that.

DR. MIKE: I think the concept is attractive but then I'm having difficulty about the actual implementation because if you meet the four requirements that we've been talking about, and practicability is one of the issues in which you would waive, that raises one question in mind. If there was a practicable question about getting informed consent, how is that going to affect the practicability of contacting these people to get an opt-out? And then I think more importantly, from my standpoint, is that if you've met all the other conditions and then you add these other things that people should consider, and there's minimal risk, there's a practicality argument, there's a rights and welfare thing, then what experiments are we going to apply this opt-out thing to and what directions are we going to be giving the IRB to say that even after you've done all of this, you still should have an opt-out provision? And I suppose one you argue that, if that's what you say, then after you've gone all through that you should have an opt-out provision for everything that has passed that screen. So, I'm just sort of—I would get confused by this direction about how I would pick and choose which projects I would require it of.

DR. SCOTT-JONES: I suppose I'm still bothered by the language requiring that the investigator contact subjects to allow them to opt out because you never really know that you've contacted them. The nonresponse means that they're okay with being in there, but you never know that you actually contacted them, and I suppose I would fear that what would happen in practice would be that studies that really did need consent somehow got put into this category of the opt-out instead of getting consent in the usual way, and I suppose if the study didn't really require consent maybe it would be better to let it go without having this step, because you never can—you never have any documentation that you actually contacted the participants. You never know that they've gotten a letter or that you were able to contact them. But if you want to go to the trouble of contacting them, why not get consent? It just seems to me to be too possibly open to studies being moved down into this category that really should have consent.

DR. LO: I would agree that it's important to make sure that this isn't the back door to getting out of consent, but maybe what we should do is go back to the transcript from Portland and actually use Mary Claire King's example. As I remember, it was a big genetics of breast cancer study, where people had previously given informed consent to a study and now they wanted to extend the study, and I'm blanking on the exact extension—whether it was a longer follow-up or a....

DR. HANNA: It's going from a marker to a gene.

DR. LO: Marker to a gene. And she was concerned enough that she went and talked to representatives of the community who were Ashkenazi Jewish saying, you know, is this going to be a problem? They said, "No, no, we want you to do the study." She felt concerned enough that she said, "I'm not happy just doing that," and I think in that sort of situation you should say it's a good thing to take the effort to try and contact people. To get back to the practicality issue, she would not do—she said she would not have done the study if she'd gotten less than a 90 percent of the samples to be studied because the power of the study and the numbers would have been compromised. So, had she used an opt-in procedure, knowing that she'd never get that degree of people returning back the opt-in papers, she would've said, well, we're just not going to do the study. So, I think that the practicality is not that you can't contact them, but you're not going to the response rate that the study design requires to make a scientifically meaningful and valid result, and therefore there wouldn't be any point in doing the study if then you couldn't possibly get any information.

DR. MIKE: Can I just make a comment on that?

DR. LO: You can give the example, because that might help people because when you—as I recall, when we heard the example, the response was, "Yes, it's good that you did that." It's not that, you know, you were wrong or morally obtuse. But it's not coming through in the abstract discussion about—

DR. MIKE: But that's not a good example, because what you're describing is a situation where she really would have liked consent, but found that it might affect her experiments or it would not be a worthwhile experiment. We're talking here about an additional requirement when there is no requirement for consent, and it seems like that thing is muddled about—misgivings about *wanting* consent.

DR. LO: No, no. I think it's important that that proposal clearly met the requirements for not needing consent. That she'd gotten prior consent for a study that was well within a reasonable interpretation to say that they gave full informed consent for this. But the original study—what we're now proposing to do is a little add-on, but—so technically there's no—from the IRB perspective, there was no sense that she was jumping out of a tough ethical dilemma. The IRB reviewers were happy to say to her, "You don't need consent for this, what are you worried about?" She went to

representative subjects and they said, “What are you worried about? We want you do the study, don’t waste your time worrying about this kind of stuff.”

DR. MIIKE: Then, why *was* she worried?

DR. LO: Well, because she took seriously some of the things that have been kicked around here—people saying that, well, if you’re clearly a member identifiable ethnic group and you’re going to do more and more studies pointing to genetic risk, there may be some group sense that, you know, the group is being singled out in a way that may cause problems with either stigma or discrimination or whatever, or self-perception. I mean, I think we have to go back to the transcript, but—.

DR. HANNA: I had discussions with Mary Claire King about this. It’s—I think a lot of it was just based on her respect for the population that she was studying. She had been working with that population for 20 years. It was important to her that she offer them that measure of respect and that they see her as somebody that was concerned about their interests. I think it’s as simple as that.

DR. MIIKE: That’s fine, but an individual investigator can always do that on their own initiative. Do *we* need to get involved to sort of institutionalize that at this level?

DR. SHAPIRO: I have two other people on the list we’re going to have to get off this subject. Alta, then Bette.

MS. CHARO: When Diane she that she was concerned that this might turn out to be a way for IRBs to loosen up the requirements for actual consent—that when consent is required they might be tempted to say, “Oh, we can use opt-out” and slide over the criteria—actually that made me perk up because I can easily imagine exactly that discussion taking place. I’m not sure that that means we want to abandon this as not a mandatory thing or meddling, Larry, but simply as a highlighted option for IRBs to recommend to their investigators, but I do think it probably argues for some language that says that to do this properly you want IRBs to really go through the discussions and confirm first and independently that consent may be waived, and only then proceed to whether or not they then want to add back in the opt-out protection so that there’s no chance of letting them slide. But they first have to firmly identify that they really could waive the consent.

Second, Larry, you asked about the triggers and what would trigger this, and the list has already begun to develop and I think it’s probably present here someplace—I forget, but, it goes—the list actually is generated, I think, by actually using not virtue ethics but the much more accessible language, although perhaps less precise—of etiquette. I really like that because good manners is mostly about putting yourself in somebody else’s position and imagining what they would want. That’s the essence of good manners. And, that means putting yourself in their position and ask, would they

actually be kind of put out? And, on political hot topics you can pretty much guess that somebody might. And on a practical level, Larry, the difference between getting consent and doing this is this only requires one mailing, one effort. Some don't get delivered, but you made an effort. You tried. That's what it's about. It's that you tried. And that's the good manners. That you tried to just let people know. You didn't have to, but it was good manners to do it even though you didn't have to.

MS. KRAMER: I'd want to go back and look at that transcript again, but my recollection is that Mary Claire King said that even though the community told her it wasn't necessary, that she had done this because she was very concerned as to what kind of guidelines we might come up with, and she wanted to make sure that she didn't—that she was not—would not end up in violation of them. In other words, she took a very ultra-conservative approach and I think she also said to us, “But be careful. I had plenty of money; I could do it.” And I think that there was implicit in what she said if not explicit that this might not be something that we would want to even think about incorporating in guidelines because it could be impractical. So, I don't know if her presentation was very powerful but I'm not sure that from that one case we ought to be making some type of policy guideline.

DR. SHAPIRO: Okay. Let's just see what our sense of this is. This is not central to what we're doing here and I don't want to take any more time on it. There is a point of view that this is just another tool that the IRB could use to be extra-conservative for whatever reason it has for wanting to behave in this way, and the concern, I guess in some Commissioners' minds is that somehow, some way, one way or another you let a thing like this out and it'll come back and haunt you in other ways and undermine the consent form. Obviously, both these things are possible. Let me just have a show of hands to see how many people think we should leave this in as a possible additional tool for IRBs or investigators to use. How many people think that's a positive thing to do? I'd say a clear majority of those that are here, so we'll keep it in the draft that goes forward. We can benefit from a lot of the suggestions made here, and so it'll be probably coming in somewhat phrasing but we'll keep it that way.

I want to now go on to a number of suggestions here that have to do with the use of the existing samples. That material is on page 199 through roughly 202. Eric or Kathi, however you want to proceed.

DR. HANNA: We tried to separate these consent issues out between those concerning existing samples and those concerning future collections. So, the first recommendation that wraps around 199 to page 200 starts to develop—it begins the discussion about the criteria that an IRB might use to determine whether an existing consent is applicable and still relevant, which will then figure into their calculations as to whether consent can be waived or re-consent is required, whether it be opt-in or we follow the opt-out measure. And we just provided some examples in here. These examples will not stay in this chapter. We just provided them for discussion purposes at

this point about some of the language that's been adopted by the LC working group and the Heart, Lung, Blood Institute in giving their IRBs guidance concerning review of existing consent documents.

DR. MURRAY: This is very good. I'd want to add one—probably a sentence to the highlighted material on page 200, a recommendation simply to remind researchers that we go on the record as saying that any cases in which subjects have explicitly refused to consent to use of their tissue in research, that that must be honored.

DR. SHAPIRO: Carol...

DR. GREIDER: One thing that struck me when I was reading through this section, really starting on 199 through 200, is that we seem to have lost the issue in the text about samples that were collected in the researcher's clinical context, and I believe this is what Larry brought up and this is where that issue came to me. If that issue does come up again in the future, samples collected in the future, but here we don't directly explicitly bring that up. The only thing is the very first sentence, which says that "Samples may have been collected under a variety of conditions." I think we should explicitly say that a lot of the times in the clinical context, the consent may have been relatively weak or bring some language to that to bring out that distinction, which has been one of the issues we spent a lot of time addressing.

DR. SHAPIRO: Other comments or questions?

Professor Capron: Do you want them on the charts? Could you put A back up, please? One of those bottom boxes there.

The result of a situation in which you don't have prior consent or the prior consent isn't applicable is stated to be "obtain consent or consider appropriateness of retaining identifiers." It's that latter phrase that I wanted to have us explore for a second—I'm not clear that what that means is "consider the appropriateness of removing identifiers" in fact, but beyond that whether it means that that's one alternative besides obtaining consent. Is that an alternative? Is it really obtain consent or remove identifiers? Or is it obtain consent, consider the appropriateness, and if you won't do one of those there's yet another option. Is that what you meant? The latter?

DR. HANNA: Yes. And then there's a section that follows this that talks about rendering identifiable samples as unidentifiable, and one reason might be because of the consent requirement.

Professor Capron: Well, I understand that, but then when you say "consider appropriateness of," you get—in the end it's either going to be you will have decided that you can get consent and you'll get it, or you will have removed the identifier. I mean, you could just as well say "consider appropriateness of obtaining consent or appropriateness of removing identifiers."

DR. MESLIN: I was just going to add in that although this colorful overhead contains larger text than the chart which appears in the draft in front of you, the chart which appears in the draft in front of you has a series of boldfaced questions which are designed to elicit the answers that Professor Capron was asking for. The short answer is, “Yes, Alex, do one or the other,” but in order to get to that answer such questions as how and when should subjects be recontacted to get consent; how should consent forms be designed to provide adequate protections for human subjects; and under what conditions is it appropriate to remove identifiers from existing samples—the answers to those questions should be in the text, which would render this more colorful chart easier to decipher.

MALE VOICE: It would be easier to decipher, but why can’t it just say what we.... Are the things which are in boldface on this chart that we have in our book things which you think we have to address because they aren’t in the chart now?

DR. MESLIN: Yes. Or for which we would like to have clarity from you.

MS. KRAMER: Will they be retained with the charts as lead questions for the IRB, or is this just for our purposes?

DR. MESLIN: We haven’t decided. If you think it’s helpful for the chart to contain the questions, that’s fine, but that’s an aesthetics issue. The questions will not go away. They may be contained elsewhere in the text for convenience. If they’re all in the same chart, that’s fine. That’s a graphic design issue more than a conceptual issue.

MS. KRAMER: Okay. I wondered if it might be helpful to the IRB in thinking through or in addressing their own questions.

DR. MESLIN: You’ll see again in the table version there are numbers associated with the boxes, and those numbers are helpful guides for the questions that follow below. Those are not on the overhead, not here.

MR. HOLTZMAN: For those of us who can only handle one question at once, are we specifically—aren’t you asking for guidance here specifically to the question in 3B? They want consent; consent is necessary; there are consents in play. How should the IRBs interpret whether or not they constitute sufficient consent? Let’s try to answer *that* question first. And then if they do or they don’t, what then happens? So, this idea of anonymizing them or rendering them unidentifiable....

DR. MESLIN: The next chart.

Professor Capron: In going back to page 200 you want us to spell out the criteria.

DR. MESLIN: Or to not spell out the criteria and allow IRBs to make their own judgments as to the answers to that question.

DR. LO: There's an issue here I think we really have to address. That's the situation where a sample is obtained in clinical context, the patient signed a blanket, all-purpose consent for the clinical procedure that, buried in the middle says, "And, by the way, you could use any removed tissue for education, research..." and whatever else the standard language is, so you've got a signature and technically there's some language in there that pertains to future research and it's pretty clear the patient probably has no idea what that meant if they ever read it. I think the question we need to address and that investigators have to struggle with—does that count under any circumstances for consent to use that sample for DNA testing? I mean, isn't that the issue that we—we can do whatever we want to do as general criteria but I think we can use some guidance on that one, and I'm not sure we've come to any agreement on that, so I'd like to see if there is—.

DR. SHAPIRO: Larry, are you following up Bernie's question?

DR. MIKE: Yes. My view on that question, Bernie, is that we look at what we just discussed this morning and up to now, but whether it's actually going to be subject to the IRB review. If it's subject to the IRB review, my view of the clinical consent form is it's inadequate. So I would have to treat that—considering that it's more than minimal risk, etc.,- I would have to go on to the next phase, which is then *what's* inadequate consent. I don't believe the clinical form where you've got that consent buried in what is essentially a treatment agreement is adequate in any way as an informed consent document.

DR. SHAPIRO: Why don't we stay on this issue, because it is an important one, and let's make sure we understand where we all are on that. Rhetaugh....

DR. DUMAS: I'm back on what Alex was bringing up earlier, and I want to make sure I understand what he's saying, that in cases where you can't get informed consent you render the sample unidentifiable and then you—you're able to use it?

Professor Capron: I think you're over at a different chart.

DR. DUMAS: Well, what are the ethical implications of that? If I don't give consent for use of my sample, then you can just take my name off of it but you can use it anyway?

Professor Capron: That's right. It's not "research of human subjects" if it's totally unidentifiable.

DR. DUMAS: But it wasn't totally unidentifiable, initially.

Professor Capron: Well, it was before I got it. The researcher cannot see the name Jones, take the name off—as I understand it—and say "I've got unidentifiable." It's a matter of—in the research design you would go to the repository and say, "Send

me samples which you don't keep identifiers on and I don't have identifiers on." That's unidentifiable by our description. There's no possibility, to use the Chairman's term.

DR. DUMAS: Yes, I was referring to a statement you made about "obtain consent or..."

Professor Capron: Well, this is part of the research design. It's not—it's not when you're in the middle of a study that you ask this question; it's before you begin the study in terms of the design.

DR. DUMAS: Okay.

Professor Capron: Could I respond to the interchange?

DR. SHAPIRO: We can come back to that issue as we get down this chart, but I do want to respond to the question Bernie raised and Larry's response. Carol and Alex.

DR. GREIDER: This is just quick. Getting back to the same issue that I just said, that I think we need to add the language of research versus clinical for exactly that reason, and under this highlighted section on 200, where it asks for us to make a list of criteria, the first thing I wrote down was, "Did the subjects consent in a research protocol or clinical setting?" as one of the criteria in that highlighted—because I think this issue is important.

DR. SHAPIRO: How do you feel about the issue? Someone is given kind of a consent that Larry talked about. Do you think that amounts to anything?

DR. GREIDER: I think it's worth—the IRB would have to look at the actual consent. I think a lot of the ones we've heard about—from the things that we've heard in testimony, I would agree with what Larry said, that are probably not real true informed consent. But there may some hospital intake forms where it is. And so I think that if that's part of what is usually submitted to the IRB, look at what was the actual consent form that was signed.

Professor Capron: I have a general sympathy with what—with Larry's position, but I found some of the discussion from the LC Working Group pointed me in a somewhat different direction, which was towards the context as opposed to worrying about the particular language in which the consent was given before. And, Carol, earlier meetings of this group convinced me that my initial instinct on this—which was there was a difference between "consenting to future research in a clinical setting and consenting to future research in what was initially a research setting"—was wrong. I originally thought, look, if you've agreed to be in research, then it makes more sense to say someone doing some further kind of research or study is dealing with someone who at least has said I'll be in research. And you all convinced me previously that that was really wrong, that the fact that you agree to be in one kind of research and that it was a "research setting" was irrelevant. Now, that was mostly—you know, we were talking

about stored tissues—that you would be no more likely to be willing to have your sample used for this new kind of research than a person within a clinical setting. And the LC statement makes the point that if you came in in a clinical setting, where you were being treated for a disease which you understand—it had occurred in your family and collateral relatives—and you’re all in for biopsies of tissue from your colon because there seems to be some kind of genetic colon disease in your family. And there’s a statement in there saying we’d like to use the sample for research and the researcher is looking at colon cancer disease, it seems to me more likely that the person from that “clinical setting” would have a “wish” for the sample to be used to determine why his or her family had a particular inherited disorder. So, they’re going from looking at the tissue to see is there disease in the tissue already to looking at it to say is there a gene that need to be associated with the disease, that the person would be—had thought, “Yes. When I agreed to research that’s exactly what I thought I was agreeing to.”

DR. MIIKE: The discussion is about existing samples; it’s not about future—.

MR. CAPION: No, I’m talking about existing samples...You’ve got a sample from a person who went in for a clinical biopsy of tissue from their colon, and they were one of a number of people in their family was going through that because it turned out Aunt Sylvia had come down with some hereditary—.

DR. MIIKE: I’m saying in general the clinical samples collected in a clinical setting won’t meet that criterion.

Professor Capron: No, but—excuse me—I think that the value of being concrete about this is what the LC did here, that to say in the absence of specific language about DNA testing, it may be appropriate to infer consent from the sources, which for the sample to be used determine why his or her family had this particular inherited disease. No one told them they were going to be looking for DNA markers because it was ten years ago and they didn’t know that they would find them. But they *did* know that they were coming in for something having to do with a familial disease they were concerned about, and they said, “Yes, you may use this for research.” So, although I start off with your assumption that that kind of blanket language is usually as useful as any other blanket language that you sign when you go into the hospital; i.e., it means nothing....

DR. MIIKE: Alex, are you using the exception to generalize through the whole clinical situation—?

Professor Capron: I’m not using the exception to generalize. I’m taking instruction from the LC Task Force, who spent a lot of time thinking about this, and saying they may have a point, which is: What if—what kinds of risks would the person have in mind when they agreed to that research. Does the IRB or the investigator looking at those consent forms think it is reasonable to infer that a person would do that; in other words, rather than saying “You may never do it,” the clinical consent that contains blanket language is worthless. Don’t bother to bring it to me. I mean, if I were a

hospital attorney and someone came in and said, “The person signed a life consent form on the way in saying ‘You may do whatever is clinical necessary for me,’ and the surgeon now wants to do a biopsy without additional consent,” I’d say, “Get that document out of my office; you know it’s worthless. Don’t even argue with me about it.” But if an IRB is faced with a stack of consent forms from people who came in for diagnostic studies on familial colon disease and you now have an investigator saying—

DR. MIIKE: I don’t know what we’re arguing about. I mean, you’re describing such a particularized situation. I’m talking about the general clinical consent form.

DR. SHAPIRO: Okay, let’s see what some others have to say about this. Alta, then Carol, Bette, Steve.

MS. CHARO: It seems to me that a way to synthesize these points of view might be to do the following: To instruct IRBs to understand that previously obtained consents, whether in clinical or research context that were not particular to this protocol, will be presumed to be inadequate for this one unless the investigator can show why it is. And, that opens the door for the exceptional circumstances, whether in a research or clinical context, in which people can be, after some discussion, judged to have genuinely intended that this particular kind of research now under review be covered by the consent they gave at that time. It allows for a highly individualized context-specific evaluation, but it starts with the general presumption that consent that wasn’t given for this protocol is not consent to this protocol, and so you show me why it is—and lets everything else then be very case-specific.

Professor Capron: I agree.

DR. GREIDER: I agree with Alta.

DR. SHAPIRO: Bette....

MS. KRAMER: I agree with Alta, unless we want to say and particularly for samples captured in the clinical setting. But I—

MS. CHARO: I think in the IRB discussions that will be one of the factors that’ll go into their assessment of what people genuinely intended at the time and whether it overcomes the presumption that this was not on their minds.

DR. MIIKE: Harold, can I just comment on that? I don’t think we need to be that specific. Any IRB that’s worth its salt will take a look at the clinical consent form and say, “This doesn’t have any relationship to this particular project.” So, I don’t think we need to even set that as a guide if you just sort of saying that you’ve got to look at the past—all I’m saying is if you look at past consent documents and match it up against what’s proposed, I am willing to bet that a whole or a great majority of the clinical consent forms won’t pass muster. That’s all I’m saying.

DR. SHAPIRO: Steve....

MR. HOLTZMAN: The urgent issue which prompted the formation of a subcommittee 18 months ago was this question, and it's kind of striking that here we are sitting and saying, "Well, what are we going to do about it?" And so I think Alta's put forward a recommendation. I don't think you can judge whether that's—we should accept that until you follow through with the consequences, because what we all recognize is most of the stuff on the shelf came through the clinical contexts where, as Larry points out, the consent was thin at best. So, most of the studies that would concern us are ones where consent is necessary, that thin consent does not suffice. So, now you either say you have to go back and re-consent—which would be often if you take that paradigm cases will not be possible because most of those people are dead, or alive but difficult; the second case is you don't do it; or, the third is you render them unidentifiable. We have a very, very stringent sense of unidentifiable which we have put in play. So, before I can agree with your way of handling it, you have to play through the implications of what we've adopted on the other end.

DR. SHAPIRO: Alta....

MS. CHARO: I think that's entirely fair, okay? If we're going to take seriously the idea that research with identifiable samples on living individuals that poses more than a minimal risk or adversely affects their rights and welfare should not proceed without consent, I don't think we can escape the conclusion that an enormous amount of material now stored in repositories will not be usable until consent has been obtained for—in some fashion, or rendered it unidentifiable, with all the concomitant loss of potential scientific value that that entails. Right? Either you can't do the studies at all, or you can only do them imperfectly. This is the nub of the problem; it has been from the beginning. It's—in my mind, it's the nub of the problem in the capacity report, and we'll talk about it tomorrow; and about no research more than minimal risk without consent. It's the nub of the problem in human subjects protection to begin with because from the very beginning when people thought that human subjects should be used only when they volunteered with adequate information, the response was that you were going to shut down important research if you insist on having any degree of information or consent on the part of the subject. And, I feel like we've lived with this decision to go by the self-proclaimed moral high ground before and I would like to argue explicitly on the record that we should do it again.

DR. SHAPIRO: Eric....

DR. CASSELL: I think it's that—it's not necessary that scientific research go ahead at all times; it's just not necessary. It's one value among others, and in this instance another value takes precedence. I think that's the issue. There goes my phone.

DR. SHAPIRO: See if someone agrees with you. If you were a true Luddite you wouldn't be carrying that, Eric. Excuse me—Trish.

TRISH: I'm sorry, I tend to agree with Eric.

Professor Capron: I agree with Eric. There's one additional issue that's raised by the material on 200 and 201 that we haven't discussed, and that is the suggestion that the subjects, although they're not required to consent because their prior consent was found to be adequate for this new study, would be informed about the test results, and that then leads into the Heart, Lung, and Blood Institute's statement of criteria, which struck me as good criteria but relevant only really in the context of that follow-up step; in other words, that one wouldn't expect. You were putting these forward as things that we might want to consider, and I would consider them in that context and be happy, indeed, quote from them as good criteria, not for the question the adequacy of the—the necessity of the extent but looking to the future of what's going to happen when we reveal these results.

DR. SHAPIRO: Alta....

MS. CHARO: I want to follow up, also, with one other thing in response to Steve's comment, because it could leave the impression that the only choices are to obtain new consent or to render unidentifiable virtually all the samples out there in order to facilitate any research. That ignores the large category of minimal-risk research that could be carried out without consent. And that in turn is a reminder to emphasize again that minimal risk incorporates in it not only the notion of the level of the harm, kinds of harms, but also the likelihood it will occur so that stringent efforts to prevent any harm from coming to somebody by virtue of the use of their tissue can make it possible to meet that minimal-risk criterion and open the door towards being able to use tissues without consent, so that our insistence here on consent—on a standard of review of prior consents—doesn't necessarily make these samples virtually useless that are at the repositories today.

MR. HOLTZMAN: Let me get back and just comment. I agree with you Alta; it's just—what I was asking us to do and you pointed to another thread in the web—is you have to stand back in the end and say, "How have you constructed the web?" Because if you said "minimal risk," you set the bar very low. Most anything is minimal risk, and you set the bar very high or low or what's right for practicability and for identifiability, etc. You *can* have the consequence that I fear making. *Everyone* fears, okay? So, then you have to look at checks and balances. That's the—that's what I'm saying.

DR. LO: Let me try and jump into this with a contrary view to what people have been saying. First, I would want to stop and question whether we state as an abstract principle the notion that research is optional and erring on the side of protecting human subjects at the cost of not doing research is the preferable high moral ground. I have no concerns about that as a general principle, and I'll have the same concerns tomorrow when we talk about basic research on people who lack decision-making capacity. I think there's an alternative version of research issues that there's a moral obligation to do it in situations where there's a good possibility it'll lead to real therapeutic advances. I think we at least need to debate it. Secondly, I would say let's really talk very specifically. We've heard from a number of people the types of studies that people are proposing to do or may in fact already be doing under mistaken notions once we're in under current regulation.

So, I would like us to think of specific examples of DNA testing on stored tissue samples where you're really not going to be able to do the project if you go back and get consent, and we've heard examples from Steve about taking very large tissue samples looking for markers for polygenetic diseases like coronary disease or whatever, and so we're not talking about autosomal dominant conditions. And, the concern I remember from several times ago was not so much doing the study in the first place, but wanting to back and recontact the patients to get further information to do more refined tests or get more clinical information. But, I think we really need to ask ourselves if we—as you run

through this and see how it plays out to then go back and check with the specific protocols and ask ourselves, “Are we really willing to say that research, which is not yet done when someone goes out and gets a new sample with tiered consent—the way some investigators are now trying to do. We may set back research and we may say that’s perfectly fine because it is optional, or we may make it really hard to do even the preliminary studies. I think there’s a lot at stake here and I want to make sure we look at what we’re giving up if we follow through the recommendations that we’re making.

DR. SHAPIRO: Eric, then Larry.

DR. CASSELL: Well, Bernie, this tension between the acquisition of scientific knowledge and other human values is a marker throughout this century, certainly in the last 25 or 30 years, but the impression that—you know, when we’re giving up something it’s like there’s this piece of knowledge that sits right under the ground there and it’s not us. It’s there. It’s apart from us. And yet, in point of fact, the direction in which we move—what we consider to be valuable and not valuable—all those things are also value-laden issues and not truly objective in some higher form. So, this argument—which is a real one—I mean, if the real tension is here, but in terms of the way the century has gone and the way things have gone generally in the scientific community is as though in fact there is no higher value than the acquisition of scientific knowledge. I think that there is, and I think that when we discuss this we have to keep that in mind. Now, you and I can argue, you know, which—which advance—would have been terrible if we hadn’t made it, but we could also argue about which advance *was* terrible because we made it. So, I don’t think—I’m not trying to dismiss it in this quick interchange. I think it always sits there or we wouldn’t be here, and that’s why we’re here, and just that reason, because of the tension between higher human values and the value of knowledge, although as Aristotle said, “All men by nature desire to know.” But there are those things, too.

DR. MIKE: As these discussions go on I keep reminding myself that they’re not all sitting there independently. They’re all interrelated. We’ve got a whole web of checks and balances before we even get to that particular position. You’ve got to get past the minimal risk—and, we’re never going to be in a position to say precisely what each of those parameters are. So, there’s going to be a lot of room for interpretation.

Lastly, if we are indeed using any research where it’s not a one-shot deal with a particular tissue but you want to continually go back, that argues more strongly on the part that I want to know. If that’s my tissue and you’re continually coming back for information, that’s a strong argument that we need people to go and say, “Yes, you can continue to do that.” So, I’m not that worried about—I don’t think it’s a dichotomy between individual rights and research progressing. I just think that the web, again as I say, that there’s enough flexibility and enough points in there that we really don’t have to—I think we’re overblowing the case here.

DR. SHAPIRO: Alex....

Professor Capron: I would add to this that, in agreeing with Eric. We are a particular institution within a web of other institutions, to use Steve's phrase, and the eventual shape of the process is one on which we only can put certain weight in, and it seems to me that it is likely that the voices of those who would cry that research is essential to the most important human good, which is the advancement of knowledge and the conquest of disease, those voices will be heard loud and clear. And they are powerful voices. And they have much persuasive ability within those who form public policy, as well as those who administer those policies through our private research institutions and so forth.

In effect, someone trying to reach a balanced view on all this might at some point say, "Well, what do the ethicists say about this?" And, if the main thing the ethicists say, as I think the present framework of our report at—in its opening pages—is that research in this area is terribly exciting and enormously valuable and gives benefits to millions of people, which is how—if you pick up this report you would think the first few pages were coming from NIH and the National Academy of Sciences to Congress asking for more funding in this field or, within this area, more liberality in the rules so that private enterprises as well can blaze forward. I think we ought to see ourselves as focusing on those values which history has taught us, as Eric says, in this century are often neglected and try to speak up for those values knowing that we don't want to seem unbalanced, that we give due recognition to the reasons people want to do this research, which are good and valuable reasons. But, if we had to err one way or the other, I think it should be towards putting the importance of taking the interests and welfare and all the other concerns about social harms and wrongs, that those get very carefully attended to and then we put the balance there. The present regulations say you need consent if you're dealing with research that is more than minimal risk with subjects, and what we're trying, in this point 3 here, to say is, "Is prior consent enough?" And I agree that the view should be, "Usually you need consent for this research; if you think otherwise, explain why." And if that seems too much on the side of protection, there will be others who will talk about why what we have said is too burdensome and make their arguments. We don't have to take all the possible counterarguments and weigh them ourselves. We ought to speak up for this set of values in that debate.

MR. HOLTZMAN: First off, I think it's important to be clear that the example people have been using of going back—in terms of the issue of re-consent or whatever, people saying, "I'm going back to the individual"—that need not be at all what we're talking about here because of our definition of "identifiable." It may have nothing to do with going back to the individual. So I use an example and I use a non-genetic example since it comes up in nongenetics and do an initial study to look at sexual transmission of disease—chlamydia—and I get the consent for it. Okay? Fifteen years later, ten years later, people start pointing out that chlamydia infection might be very important in the

formation of heart disease. It'd be very interesting to go back—not talk to the people but ask the question, “Those folks from whom I got that initial sample, did they develop heart disease?” I don't care who they are. I'd never know that it was John Jones and Mary Jane and everyone else. But, the way we've rendered it, unless it was severed I can't get that. Okay? So, it's not a question of going back to the person the way we've set up the issue.

DR. CASSELL: Well, what are you going back to?

MR. HOLTZMAN: I just thought I'd want to go back to the record, right? But I can't go back to the record because we've defined that as identifiable because there was a code.

MS. CHARO: Right, so you have to go back to the individual.

MR. HOLTZMAN: That's what I'm saying. So, that—what we're saying is when this breakthrough comes through, it's suggestive, because I'd like to look at the record. I'm not saying it's right or wrong.

Professor Capron: How would you get to that record without their consent? It's not attached to their chlamydia file, as it were. You have to get—

MR. HOLTZMAN: You're not listening.

Professor Capron: I am listening.

DR. CASSELL: I hear the same question.

MR. HOLTZMAN: I do an initial study in which I get the samples, with consent, for example. I do that study, right? Ten years later, the potential link to heart disease comes out. It would be interesting to tie together the subsequent outcome data if you will give these people...

DR. SHAPIRO: You want to go back to the medical record.

MR. HOLTZMAN: You want to go back to the record—you want—you don't even—

Professor Capron: Why do you want to go back there?

MR. HOLTZMAN: What you want to know is the samples that tested positive—did they then correlate—

DR. CASSELL: Where are you going to find out about heart disease!?! Don't shake your head! Where are you going to find out about heart disease?

MR. HOLTZMAN: From the medical records.

DR. CASSELL: Ahh! I don't have any say in whether you go back to my records?

Professor Capron: I thought you were asking a practical question. I went into a Sexually Transmitted Disease Clinic and they found I had chlamydia. They have that record there. Where is my medical record on my heart disease? That's not with that clinic. I'm not even living in the same town. You're going to have to go back to me, find out where I'm getting my health care, and look at my records.

DR. SHAPIRO: Alta....

MS. CHARO: I'd like to continue to try to answer Bernie's challenge, because regardless of the details, the hypothetical that you raised, Steve, it's really about Bernie's challenge. And I recognize the interest that we bring to this table. I mean, you work in a company that I'm going to presume has a very big financial stake in how this kind of stuff happens because research that can or cannot go forward without consent will in turn determine the scale of the research that's possible and the kind of investment one's going to get from the private sector. Many people here are investigators whose livelihood depends on getting grants to just this kind of research. Some of us are kibbutzers whose very salaries depend on having something to complain about in print. And all of us are potential human subjects whose records are going to be used. So we bring a lot of interests to the table when we debate this kind of balance between scientific research that's relatively unimpeded and these kinds of standards of personal control that we've elevated the level of—highest principle of autonomy. I don't know that we could ever actually weigh these two together and determine that one is more important than the other intrinsically. But in a more pragmatic way I would suggest that over the very long run, because I think it echoes things that Eric and Alex and others have been saying, we depend completely on the trust of the public in the research enterprise. And while this year, in this decade, genetic research and tissue sample research seem to be the key to everything, twenty years from now it'll be something else that seems to be the key area of research, and the long-run question isn't going to be did we benefit sufficiently from this era of research and tissue samples, but the question is going to be in the long run, do we have the public's cooperation and willingness to go along with a large-scale research enterprise? And when we seriously contemplate allowing a slide-by with a legal technicality because somebody signed a consent form—we're going to call that genuine consent and allow ourselves to slide through this difficult discussion by suggesting that prior consents might be usable, as one option. I find myself very uncomfortable because if anything's been demonstrated this last week in Washington it's that, you know, technical, legal interpretation of documents and words are not going to engender a great deal of public trust and we don't want to make that kind of mistake. The last people we want to be in control of this question are the lawyers. And we really want to go for the heart of it, which is that whatever it takes to have the public go along willingly is important to maintain. The fragility of that trust as witnessed through the radiation experiment furors and the Cleveland *Plain Dealer* furor has been evidenced and I don't think we can afford to make that trust any more fragile than it is.

DR. SHAPIRO: Trish....

MS. BACKLAR: I think there's another way, also, of looking at this. I think it's very difficult to compare and contrast the general; and the particular and the partial. And I'm thinking even in clinical care, the patient in front of you is going to be the person you're going to have to be thinking about. You may be looking at that patient in a general context. You may be in a closed system like a single-payer health system, but you're still going to have to think about the effects of that care on that particular person in front of you, and I think it's the same thing in research. There may be some generalizable knowledge, which is going to benefit this person in front of you; on the other hand, those particular subjects who are going to donate themselves for that generalizable knowledge, you need particular and partial care.

DR. SHAPIRO: Bette and Carol.

MS. KRAMER: I'm trying to diagram this for myself, and I hope somebody will tell me where I'm wrong if I'm wrong on this. If we deem the prior consent invalid and say you need to go back and get consent, if the person is still alive, either they're going to give it or they're not going to give it, so you're going to get it or not get it. If the person is not available so that you can even try to get the consent, then that's when you would end up stripping the identifiability, right?

DR. MESLIN: No. You can't use the sample.

MS. KRAMER: What—you can't use it? You can't use it; you can't strip it? I thought that you could. I thought that's what you were saying. You could then strip the identifiability and use it as unidentified.

DR. MESLIN: If you try to get their consent but you can't, then you can't use their sample unless you then have your plan for stripping, which we haven't come to yet. But based on your diagramming, if you require informed consent and you try to recontact the person and they say, "No," then you can't use their sample.

MS. KRAMER: But if they're not available.

DR. MESLIN: Then you can't use their sample, because they haven't given you consent.

MS. KRAMER: Even if it's stripped?

DR. MESLIN: Well, if we're doing it in phases, the answer so far is no. Then we'll decide whether there's a plan for—

MS. KRAMER: Nonetheless, could not a repository supply to the researchers those samples along with the information—pertinent information from the medical records in a stripped fashion for use in unidentifiable research?

DR. MESLIN: So far, yes.

MS. KRAMER: But it could be provided. Is that correct?

DR. MESLIN: Yes.

DR. GREIDER: It's not within one protocol, right? It's not like some of them consent, but some of them don't and they're stripped. There's a different—you'd then go back and you strip all of them and the entire research with stripped samples. You're not going to have a mix of some stripped and some not stripped. Right? It puts you in a different box than that last....

MS. KRAMER: I'm trying to—you know, I guess I'm trying to get a handle on this in terms of you've got all this tissue that's archived. Some of it goes back a hundred years, eighty years, fifty years, forty years. You can make the presumption that a lot of those people are no longer alive and that therefore under no circumstances would you be able to get consent from them anyway. You can use it, but it's stripped?

DR. GREIDER: No, no, no! You can use it with an old identifier. Once they're dead, they're not considered human subjects.

DR. SHAPIRO: Carol and then Bernie.

DR. GREIDER: I want to get back to this issue that we were discussing. We had a little bit of a discussion here, which started with Steve's statement that if what Alta had proposed, which is setting the moral standard high, were to be adopted, that a large amount of research on stored samples that are sitting in repositories won't go forward, and I just want to think through whether we really think that is a true statement or not, and maybe Steve could help me—to give me an example of why you felt that was the case because, first of all, there's all the previous discussion that we had this morning that a lot of research is going to be done because it's being considered minimal risk. And so a lot of the kinds of studies could go forward, anyway, because it will fit in that category, and so are we really discussing a major issue here or not?

MR. HOLTZMAN: I think that is the right question. All I was saying is so you have to go back and ask, "What now will fall in the category of minimal risk?" You ask to see how broad the bucket is. And if there's been a tendency to say we should construe risk in a protective sense, because probably in Eric's type of argument that we will want to err on the side of safety, you're going to have more things that fall in the category of greater than minimal risk.

Now, what Alta suggested as a sort of a counterbalance to that, or when you multiply the level of risk by the probability of risk if you can the lower the probability via confidentiality schemes, encoding schemes, well, then you may still be able to then bring things more back within, but we had a long discussion about how should we construe minimal risk, where we tended to say that in some ordinary language sense, we want to view it in terms of the nature of the risk and separate that conceptually from probability of it occurring. So, I'm just saying you have to bring those matters all together. I can't

answer your question, Carol, until I see how we as a Commission came out on every one of these things.

DR. GREIDER: I just wanted to clarify that. Just because we seem to have split into a conversation about this sort of more high-level, philosophical issue, if you will, of individual protection versus research going forward, and I didn't really feel like we'd gotten to that point yet. I wasn't with everyone, really having to make that decision yet at this point with this issue that we're discussing.

DR. SHAPIRO: Well, let me try to see if I can try to characterize where we are. We are going to have to move forward even as we struggle with this issue. There is the point that Steve made that whatever we decide on this, and whatever we decided on some of the previous ones, at the end of the day we have to look at the system, and it may tell us something which none of the individual components have told us. So, that's, I think, quite correct; it's absolutely something we'll have to be conscious of. When we have our drafts that we're ready to send up on the Web, we'll be able to assess—others will be able to assess—we don't have to resolve that issue. It has to be resolved, but we don't have to resolve it today, and we'll have lots of input on the assessment of that kind of general equilibrium problem, if I could use those particular words. But it's a very important problem.

There is a second issue, which has taken up most of our discussion here, which started out with the issue of whether these general blank checks, as we call them, really amount to anything, and the general consensus of the Committee was, they don't amount to very much, and therefore we need to find some way to—and some appropriate way—to let IRBs know that they have to think of some additional consent of some kind here that's going to be required if you want to go ahead. And we have to think that through. Alta made a particular suggestion about how that might be phrased in a general way; that might be very helpful. So, I think what we have to do here is go back and try to rephrase it. I do take it as a sense of the Committee although not a unanimous view of the Committee. The one—the blank check—is not sufficient. And that the presumption ought to be that some form of consent is required here—some form of *additional* consent is required here in order to proceed if the other barriers have not been exceeded, if it's more than minimal risk, etc., etc., I don't want to review that long list.

Now, it's my own sense that we will have to be extremely careful—and this way I think I feel somewhat the way Alex feels. We have to be more careful about giving away an ethical argument for the purpose of not getting in the way of research, than the reverse. Now, hopefully it'll be somewhat balanced. But if we're going to err anywhere, we have to err on the side of bringing to the fore what we believe to be the important ethical issues. We'll have all kinds of people telling us what we're doing wrong. We don't have to worry that no one's going to notice or that we won't before we get to our final report have some kind of view as to whether we've somehow blocked all the benefits that people are going to get from the scientific research, which most of us are

committed to one way or another. But I do think that the balance we have to reach here, the perspective we have to have on this, is to bring these other issues to the fore, look at how it impacts our overall scheme, as Steve has pointed out to us, then let's—as the expression goes—put it out there on the Web and see from others who perhaps know more about some of these things than we know. So I think that we'll have to restructure this in some way, but I do—we do have to get past—this is a critically important issue. We can't put it away for all time today. So, I'm glad we spent time—more time than I expected on it. That's where I sense we're going. Bernie....

DR. LO: I'd like to make a few procedural suggestions. I actually think this is an important discussion, and it's a very important issue that we need to think through, and I completely agree with people who say that we have to look at how our little decisions on each issue add up to sort of a web or system. I guess I would urge us to, as we think about this, to go out of our way to invite people actually working in the field to give us specific examples of studies on existing samples that may be problematic and to help us think through how our suggestions would affect their ability to do the study. They may say, "You're absolutely right. We shouldn't be doing this. It's a bad idea. Thank you for letting us know." But we also need to understand what kinds of studies are going to be much harder to do. I think we need to understand issues like minimal risk. Many of us have pointed out, you know, you can compensate for a tougher definition prior to consent by loosening up your definition of minimal risk and vice versa.

I'd like to have people give us examples of prior consent forms that they think justify the exception to Alta's presumption. I'd like scientists to tell us what sorts of sacrifices in particular—scientific sacrifices you would need to make in order to—if you're going to strip identifiers in order to do the study under the right-hand column. I mean, I think you're right. We need to put it out there on the Web and see what happens, but we have to ask very specific questions, like we're really interested in feedback on these particular issues.

DR. SHAPIRO: That's certainly a good idea. Larry....

DR. MIKE: I don't really think—I'm just recollecting that Dave Cox, Carol, Anne, and Steve said that the real research in this area is longitudinal studies, where you've just got to go back and back and back and get more information. If that is so, then the great majority of important research in this area, which is beyond minimal risk, has an independent need for getting informed consent, which is that you're going back and back and back and getting additional information. So, I don't think it's going to be that big a problem if what they tell me about where the important areas of research are going.

DR. SHAPIRO: Thank you. We will try to—however our recommendations get articulated, we will try our best to get people who we think might be impacted by them to take a close look at them and let us know if there are issues we haven't seen. Okay.

Let's—Eric, do you want to take a look at the recommendation that comes to the bottom of page 201, 202?

DR. MESLIN: In effect, the recommendation regarding disclosure, etc., is part and parcel what we've already been mentioning. This is where Carol and Bette, I think, were going previously. I think the only thing that probably needs saying there is we have laid out a number of options, principally on page 202, and these are a summary of collected options that have emerged from those presentations which the Commission has had from various organizations and individuals. So, we are providing a set of suggestions there for what various consent options might be. And, this is for your consideration, with the exception of "D," by the way, which Harold's already said something about—the blanket of consent—but we'll leave it all open on the table.

DR. HANNA: I think it's pretty self-explanatory. These are just, obviously, just as a reminder, this is for research where the waiver of consent has not been granted and where it's deemed that the existing consent form is either nonexistent or is inadequate. So, here are the various options.

MR. HOLTZMAN: A quick question. A lot of these options are phrase in terms of going back to the subject. The—as opposed to the repository just simply saying, I'll anonymize it. And therefore it'll no longer be human subject research.

DR. HANNA: Going back to the subject would be explicit intent to either get consent or get dissent, not to go back and get additional information or whatever.

MR. HOLTZMAN: No, I understand that. So, do we have here—you're laying out the options, right? And I don't see an option—maybe I'm just missing it—in which the investigator of the repository or whatever says, "I'm not going to go back to the subject at all. I'm simply going to anonymize the sample, rendering it unidentifiable." Are we saying that's not an option?

DR. HANNA: It *is* an option; it just happens to come later in the—it comes on page 206.

DR. GREIDER: I just have one point of clarification—I don't want to go into the wording now, but as I read the three lines on 201, 18, 19, and 20, I have a very hard time understanding what they mean. I understand now that you just said what you said, but I don't think it said that in the language used to clarify that. I was very confused by what this is even about.

DR. SHAPIRO: Bernie....

DR. LO: It seems to me that this—the discussion on page 202 boldfaced should be very similar to—identical to the discussion for prospective future collections. And, one thing I would like to see in this section 202 is the option of tiered consent or layered consent. I think just to say, you know, "blanket consent" without some sense that you

may consent to some things but not others so far—that’s where a lot of the activity’s directed now on the part of researchers and advocacy groups I think, to the extent that that may offer the best solution to a meaningful consent, we ought to play it up here.

DR. SHAPIRO: I agree with that.

DR. MURRAY: I’m just reading this over. A and D, for example, are not mutually exclusive, at least, as I remember it. It’s not either/or. I actually like Bernie’s idea of trying to have this parallel, in which case I think it would be most appropriate here to, if we want to instruct the staff to try to—you know, just—I think you’re very much going in the right direction. Just redraft this a bit and limit our comments at this moment, given the shortage of time, if we have something very central and substantive about this point that we want them to bear in mind as they redraft.

Professor Capron: You would see these as a spectrum in certain ways. The order is really D, A, C, B—basically saying, “You don’t have to come back to me at all, even with a—give me assurance and I’ll hear if there are results of clinical importance,” consenting to the specific protocol, consenting if it’s unidentifiable, and saying, “never use it.” I agree with Tom—we could say “and/or” at the end between C and B.

MR. HOLTZMAN: I just want to second Bernie, effectively by defining the premises here. You’re dealing with what is tantamount to a new study—as if you don’t have an existing sample, and maybe that’s the simplest way to say this, as opposed to trying to make sure they mirror each other.

DR. SHAPIRO: Okay. There’s a hint at the bottom of the next page. I don’t know what to call some of these questions that are in our text, which says we may wish to develop more fully discussion on the “special scrutiny” category of research. Let’s see how people feel about that. Kathi or Eric, you may want to say something.

DR. HANNA: Well, I think the special scrutiny category kind of resurfaces periodically throughout the chapter. And, again, it might be determined that the existing consent form *is* applicable; however, for other reasons you think this protocol deserves special scrutiny and therefore you might want to—I mean, again, we get—I don’t think we’ve defined yet what those other reasons might be beyond concerns about minimal risk or adversely affecting rights and welfare. It’s this kind of vague other category that does it concern potential harms to others, does it implicate groups? There might be a lot of things that fall into that special scrutiny category. So, it’s just—special scrutiny issues seem to come up every once in a while, so we just highlighted wherever it surfaces again.

DR. SHAPIRO: Alta and Diane.

MS. CHARO: I want to just put on the table one possible way of going about this, but I’m not real sure that it’s necessarily the best. Frequently you find guidance to bodies that says, “You got to figure it out yourself because we want you to do whatever was asked that you do,” so we have determined that. Whenever you have this kind of

group—and then they give a list that says, “including but limited to,” so that you give them free—you give them free rein but you also give them concrete samples. And the concrete samples that immediately came to mind—if we were to use a list to get started, to give people concrete ideas—included protocols relying on groups made up of specific ethnic, racial, or religious groups; protocols examining the diseases associated with sexual activity; protocols involving reproductive organs and tissue, gametes, embryos, and fetuses; and protocols that are looking at any kind of addictive behavior. And then I put in huge question marks a fifth possible category for the “included but not limited to” list of protocols that are examining mental illness. Keeping in mind the many comments we got about not wanting to overly stigmatize but at the same time recognizing the existence of stigma. And—this is a kind of compromise—we can try to come up with a good definition and try to come up with an exhaustive list.

DR. SHAPIRO: Eric. Excuse me—Diane. I apologize. You’re next, then Larry, and then Bernie.

DR. SCOTT-JONES: The category of special scrutiny bothers me a bit, although I understand why it’s needed. The suggestions that Alta just made were good. It seems to me that one doesn’t avoid research because the subject is controversial, and I think that that notion just won’t sit well with most people, that you should avoid research because it’s controversial. So I was wondering if maybe in addition to the kinds of things that Alta mentioned, we could say something about past harms from the way research has been done. I’m not sure, but just the notion of special scrutiny because something might be controversial is not the best hook or the best way to get to the goal of this.

DR. SHAPIRO: Okay. Larry.

DR. MIKE: I understand special scrutiny category to talk about a stronger, more select consent process. I’m afraid what this raises is a specter of our opt-out provision, and the discussion that Diana’s worried about and what our current draft says that opt-out is not related to consent. Well, if we’re going to have an opt-out provision, I think we also have to deal with what do we mean when we opt out, and we’re going to do a special scrutiny of those areas in which we’d want to opt out. So, if we talk about special scrutiny, we unavoidably get into what kinds of things are we going to say need an opt-out provision and what kinds of things are we going to need a more selective consent provision. So, now the two are bound and so I don’t know what the dilemma is—I mean, I don’t know how to get out of that dilemma. But if we’re going to have an opt-out provision and then a special consent provision, we’re stuck with that dilemma as far as I’m concerned.

DR. SHAPIRO: Okay. Let’s go down my list. Bernie...?

DR. LO: I support Alta’s approach of giving a “for example,” a “but not inclusive” list—and I would also include under there not so much mental illness but behavioral genetics, where there has been past abuses and good evidence from a

forthcoming IOM report that the level of research done is pretty sloppy in some instances. And I would follow Diane's comment about controversial. It's not just so much that it's controversial, but these are the types of research that we can expect some individuals to have particularly strong objections to participating in. So, it's not just that it may be misused or it's a hot-button political topic, but certain people say, I just don't want my tissue—if I had a choice I would choose not to have my tissue used for that type of research, although I may well allow it to be used for all kinds of other research. So, it's a way of recognizing that autonomous choices, to the extent we can make them meaningful, are even more important in certain types of research involving DNA genetic testing as well as other types of research. And, again, Larry's point that there are lots of different ways to get out of that and the opt-out is only used in a situation where there is sound justification for not doing anything at all. And we're saying, well we want you to do a little more than that for just the reasons Alta—as Alta was saying before—we want to err on the side of protecting people in the sense that they could feel wronged if not outright harmed if their samples were used in certain types of research.

DR. SHAPIRO: I have to confess, I myself have very ambivalent views about this particular special scrutiny category we're trying to construct here. It's very convincing in cases that I hear you talk about here. But then I start reminding myself that this is—if I understand our web well enough—that this is research which has already satisfied all the rights, welfare, etc., etc. It's all satisfied. And yet there's still—on top of that, somebody somewhere sitting says, “There is in addition something else that doesn't come under rights and welfare, don't come under minimal risk, don't come under one of those things. And we have determined that somehow additional.... I do have an unsettled mind about this. I'm not yet convinced on either side and I find myself in an unfortunate position of agreeing with the last person that talked. That's a dangerous sign. So I apologize for interrupting, and Tom—

DR. MURRAY: You threw me with that comment, now. Can I wait to be the last person? I guess on the whole I favor the special scrutiny category, the reason—the primary reason being that all the other stuff effectively deals with the individual, harms to the individual, whereas the special scrutiny springs into operation when you talk not about individuals in isolation but rather something about them as members of a group. A group of people is a small group of identifiable people. They are—a number of them have agreed, they don't have any in-principle objection to research of tissues. However, they have a very important origin story they tell about themselves. They've given blanket consent—each individual has—and the researcher proposing to do it could in fact threaten that origin. I would like IRBs to say, is that something we'd really want to do without going back to people and saying can we get your consent—that's a case one can imagine. I think Alta's notion of giving a list is an excellent one. We should preface the list with a statement like Bernie's. It isn't that the research is controversial; it's that research to which people might have objections because of something about the nature of the research or the expected outcome. And then give some examples,

delimited—including but not limited to. I think that makes sense. Then we still have to decide if you—if you’ve referred it to the IRB for special scrutiny, what do you do with it—should the IRB do with that? Here we turn the page and I’m not sure we have the only answer on page 204.

DR. SHAPIRO: Okay. Steve, I still have you on my list.

MR. HOLTZMAN: I want to make sure I understand the staff’s recommendation. So, we go back two italics before, and we deal with a paradigm case of the sample in the repository where it was gotten under a general consent, right? And I think we’ve concluded that that general consent—since we use “gemische,” we can use another Yiddish term, the general consent is worth bobkes, right? So we start there okay? So, if the general consent is worth bobkes and you’re in an area where you’ve got a re-consent, clearly we’re not recommending in here in this italic, “opt out.” So now we go on back to the individual under your next set of italics and we’ve gotten from them a general consent? And now the recommendation is to layer on top of that second general consent, as it were, the opt-out as well for special scrutiny. It seems that if you were back getting the general consent the second time, one might have said, “There are various categories of research which you may or may not find objectionable.” Did I get it right? Is that what you were saying?

DR. HANNA: Yes. There are two kinds of opt-outs, and we probably shouldn’t use the same term for both situations.

DR. SHAPIRO: Okay. Thank you. Alta.

MS. CHARO: On page 204 we’re talking about opt-out in these various senses. I think there’s an entirely distinct situation which the special scrutiny category could be used, and here I want to just reference my lunch-time conversation with Karen Rothenberg from the University of Maryland. We talked about it a lot. Where research—and this—we talked about it before—where research is being done in such a way that the source of the sample—the individuals out there in the world are totally unidentifiable, but nonetheless the research is being done in a way that might characterize the entire group of people. We have struggled over the question of community and communal effects, and it seems to me that in those situations, opting out is not a realistic possibility as a response because we don’t know the individuals are whose samples are there because they are unidentifiable. But there are, nonetheless, other things that can be done, and we did discuss this at the Portland meeting and before. One proposal had been that investigators, although under the current multiple assurances that have been executed generally are not required to go their IRB administrator and ask for a finding that there is no human subject involved. It’s kind of a self-referral thing. And on most multiple assurances, if there’s no human subject involved there is no need to see an IRB. We could recommend that they be encouraged—or some institutions might even want to require—that anybody who is dealing with human biological materials or with medical

records that describe human beings at least have a conversation with the IRB administrator about whether or not one of these categories is present and that there be conversations about ways that the study design might be changed to minimize the prospect of these kinds of group effects or that the scientific basis for the research be doubly checked. And the whole thing could be done with a very light touch as a way to have some entrée into the question of community consideration, without ever touching on the question of community consent, dissent, mandatory consultation, etc. I mean, there's a world of this discussion, that's in our transcripts now, where the special scrutiny of categories would be implicated. But it all begins by saying people who currently have no obligation to be interactive with an IRB system would suddenly be encouraged or required to have at least some minimal contact with the IRB.

DR. SHAPIRO: Okay. I have Bernie, Diane, and Bette. Bernie....

DR. LO: Harold, I want to go back to your comment a couple of rounds ago about your ambivalence about this whole notion of special scrutiny. I wanted to ask a couple of questions, really directed to all of us, as what the grounds of that ambivalence and uncertainty are. First, is there a sense that we're maybe not going far enough, that when we say "special scrutiny" we're obviously concerned and have we pegged the level of concern too low—that we really should be saying, "This is in the category of full informed consent, not this sort of opt-out middle ground." I think—Diane articulated that a little while ago in another context. I think we need to think that through. I mean, we're proposing this as a middle position, and part of the discomfort is that maybe it really should be bumped up to a higher category.

Secondly, is the source of our ambivalence and dissatisfaction that we can't really articulate clearly yet what it is about all these things that makes us group it together and separate it out from an awful lot of other studies? And is it our concern that somehow we're missing something we should be able to articulate more clearly; we just haven't gotten it yet?

And third, I guess, is to suggest a way of looking at this that any time we're designing recommendations for a very complicated subject with a lot of interweaving parts of the web, we should be humble and say that we're going to miss some things or some things are going to fall through the cracks. And this goes beyond the "any time you have rules and guidelines there are going to be exceptions," that there are certain situations where we have this instinctive sense we may be even more likely to need an exception in that situation than just...and we're just trying to highlight things for IRBs.

I'm very concerned throughout both these reports that we are giving IRBs a lot of new heavy responsibility. I think someone's got to do it and they're probably the best people to do it. But—it's the background. A lot of concern that IRBs now are stretched too thin, don't have the resources, are overwhelmed; are undertrained; don't understand; etc., etc. And so I think—I mean, that's a whole issue in and of itself. I think anything

we can do to really help IRBs in specific terms to look for caution areas or for danger spots—I think would be useful. So, that’s what I see this as being, saying that these are particular areas where you want to try to be a little bit more careful all the time, because though you’re trying your best to be careful all the time, because this is where the next trouble spot might come up. I think it’s important to try and understand why we’re uncomfortable with this.

DR. SHAPIRO: Well, first of all I wouldn’t want to say that *we* are uncomfortable. I tried to say *I* was uncomfortable. I’m not sure that anybody else besides me is uncomfortable on this, but I’d be glad to respond to the very helpful framework you’ve laid out.

It was not my concern that we hadn’t set the bar high enough and so on, nor was it my concern that—nor *is* my concern—that we might miss something, which we certainly will no matter how long we work. Life goes on and there are things that we’ll miss.

What concerned me at times concerns me since I am ambivalent about this—is that who it is that decides what’s special, and what set of forces does that respond to? And when you lift this issue of consideration up to some relatively central organization, like an IRB on a university campus, it responds to all kinds of forces up there. And it’s trying to think that through in my mind as to how that would play out over time on issues—all the examples you’ve given are controversial to somebody. There may be other examples, but I think that’s why there’s some concern. That’s what was in the back of my mind that I was trying to struggle with. That was really where my ambivalence came from.

Alex—exactly on this issue? I’ll have to go back to Diane in a minute.

Professor Capron: It seems to me actually that one of the arguments that’s long been made for IRBs is some notion of localized reflection of a community sense—the notion of special scrutiny with some examples given or some categories to think about, but basically loading this onto the IRB. Otherwise, our recommendations about the IRBs—stuff like the old line about the man who ran a discount store and said, “Well, I lose money on everything but I make it up in volume,” and we’re just—we already know the problems in IRBs. It doesn’t make sense. But here, if there is some reflection of what this community in some sense might think of and then another IRB *wouldn’t* regard that as a category of special scrutiny. That doesn’t bother me too much. What I wonder about is what are the things that we are thinking about that don’t amount to an adverse effect on a person’s rights or welfare but which do fall into a category where something beyond the waiver of consent, or if you’ve gotten consent something beyond just that consent and going back to them makes sense. And it does seem to me that beyond the group effects, the notion that some people object to categories of research or types of research results, even if their own direct rights or welfare are not implicated does make

some sense. I think we sort of capture a little bit of that within—. And as I said, I'm not bothered here by the fact that IRBs are going to react differently. This isn't being done out of OPRR; it's being done at the local level.

DR. SHAPIRO: Okay, Eric. And Diane and Bette are waiting patiently.

DR. MESLIN: Very quickly—one of the issues staff had considered in putting this together but did not make its way into the draft comes up in the regulations at 46-111, section 2, and I'll just read it quickly. "The IRB should not consider possible long-range effects that will apply knowledge gained in the research, for example, the possible effects of research on public policy as among those research risks that fall within the purview of its responsibility." It's a rarely discussed provision of the regulations and we have not had a conversation with OPRR about this and we obviously could. But in light of much of the knowledge that we have been hearing that results from the use of genetic information, this was an opportunity for us to think about types of research where the knowledge generated would not be of particular concern to that individual but might have a long-range effect on the insurance policy or employment policy, or the like, and if it's true that IRBs are prohibited from considering under—just to remind you again 46-111.a.2 on page 8 if you're looking in the back of your regulations in our guidebook, you will see that language. So, we might want—you might ask us to consider that in more detail.

DR. HANNA: Just one point of clarification is that in discussions with OPRR, they said that an IRB cannot disapprove a study on that basis. However, they can consider those issues in their deliberations.

Professor Capron: This is not—this is the part of the regulation that does not relate to what we're looking at. This is the weighing of benefits and risks of the research. We're dealing with the rights and welfare of the subject. And it's possible to say that the IRB says that a subject has—may have reasons means to object that do not rise to the level where their consent will be required, but where enough extra scrutiny is deserving that they ought to be notified that research is going on and give them opportunity to opt out.

DR. SHAPIRO: Okay, I think we want to go Diane and Bette now without interruption from anyone else, including myself.

DR. SCOTT-JONES: I tried to think of language that would be better for this section, and I believe that certainly "controversial" should not be used because scientific controversies are what research is about. And so to use that term is inappropriate, and I think that this section might be made more explicit regarding the concerns that actually underlie it because I think the language does say that, you know, there's behavioral genetics protocols or research where the subject matter is particularly controversial. I think that if we want to keep this section, it needs to be more straightforward in what is meant, and some of the things that I thought of that might possibly be met would be

studies—and this is not consistent with what Eric just read to you from the regulations—that is that studies that not only address scientific concerns but might be seen as bearing on social and political choices in society. I think we should spell it out if that’s what the issue is there. Also I think we should use language of the kind that Bernie mentioned—for example, referring to an individual—referring to the issue of choice, respecting the choice of people in society, and I think also if some of this has to do with race in our society, that we should spell that out. And I just recently saw a series of articles in the *American Journal of Public Health* that says that perhaps we shouldn’t use race at all in medical or biomedical research. But at any rate I think that the special scrutiny category has importance—but we need to do a better job of it than is here and work on specific language that could be used.

DR. SHAPIRO: Bette.

MS. KRAMER: My concern was that what seems to be the problem is the whole additional category, and I’m wondering if in examining the kinds of things that we feel are raised to that category of special scrutiny might have particular relevance—if those concerns might be captured in consideration of the rights and welfare when that comes up.

DR. SHAPIRO: I think—as I’ve understood it (and I’ve asked the Commissioners here to correct me)—that what those are people are concerned about are primarily issues that go beyond the individual. They may have trivial effects on a single individual but may be some in other way important to a group.

Professor Capron: Another category would be particular belief of the individual. For example, in behavioral genetics or abortion research or something—I mean, there are categories.

MS. CHARO: I think Diane is absolutely right that it is not about political controversy and that that gets us down a very dangerous road. I do think what it might be about is some degree of courtesy. Some degree of courtesy for people who would like not to be complicit with a particular research agenda, whether because they feel like it tarts some group that they care about or because it implicates a political belief that they feel strongly or for any other reason and that all we’re doing is struggling to give our best guess of those situations in which there might people who would say, “It’s not about me and the harm to me; it’s about my willingness to be complicit.” And that’s always, I think, also a little bit to Rhetaugh’s concerns about stripping of identifiers, that’s also part of that discussion. And maybe with that as a kind of the dominant thought we’ll be able to come up with language that’s not off-kilter the way we’ve been struggling with it.

DR. SHAPIRO: I’m going to appoint a special privilege only to Jim since he hasn’t said a word yet today, and then we have a guest here. We really must take a short break and then give our attention to our guest.

DR. CHILDRESS: It strikes me, hearing the discussion, that part of the difficulty may be calling this a special scrutiny category because it's not carefully scrutinizing the research in terms of evaluating risk and benefits, but rather offering certain kinds of opportunities for individuals to make some choices which might be symbolically significant. It might deal with their views about the long-term consequences, but we called it something else. And I don't have a proposal. We might get away from some of the issues that arise in trying to think about it.

Professor Capron: Page 189 says it might be a reason for saying that something is greater than minimal risk, so it goes beyond individual consent.

DR. SHAPIRO: We will have to wind up this discussion—further discussion by this particular report. By returning to it we'll have to squeeze some time tomorrow into it—into our schedule to return to this for half an hour or 45 minutes. I don't want to take any further time this afternoon. The approval—if there's no objection we'll take, hopefully, a very short break—hopefully it's about five minutes—and then turn to our guest C.K. Gunsalus, who is here today. She's the Associate Provost of the University of Illinois; there's a paper we have here. We've seen a draft before. And I'm very grateful that she has taken time to be here. So, later we'll turn the agenda around. We'll take the human subjects and project research plan and do that last this afternoon and we'll deal with the issue of standard models for human subjects oversight immediately at the end of our break. So please, five minutes, because we'll need the extra time.

DR. SHAPIRO: As I've told you before, we're going to make a number of changes in our agenda. First of all, I've taken the unilateral action of deciding that we will try to start as close to 8 o'clock tomorrow as we can to see if we can squeeze in a little extra time. I guess this afternoon, as I said before, we're going to move directly to the item "Standard Models for Human Subjects Oversight," for which we are very fortunate to have a paper from C.K. Gunsalus—this is the paper here. Everyone's had that at their place today. And, fortunately for us, Ms. Gunsalus, who is Associate Provost at the University of Illinois, was willing to come here to make a presentation and answer our questions. We are very grateful to you for the work itself and for your willingness to be here this afternoon. Thank you very much, and let me turn the floor over to you.

STANDARD MODELS FOR HUMAN SUBJECTS OVERSIGHT

MS. GUNSALUS: Well, thank you for having me. It's a pleasure to be here. I think the last time I spoke with you I introduced myself by telling you that I come from the "train wreck" school of professional ethics. I mostly deal with the lapses and aftermath of problems, which leads to my personal interest in effective and credible self-regulation, which is at the root of most of what I've done and most of what I've talked about with you here. I'm a very applied person; I'm not a very theoretical—I don't have

a very theoretical approach, so a lot of what I've done in the paper and a lot of what I talk about today are very pragmatic sort of considerations.

The dilemma that I think you're dealing with in human subject protection models is common to many forms of self-regulation, which is that it tends to become routine and to drift a little in the absence of scandal. And then you have scandal and people immediately stand up and there's a lot of hoo-ha and then the scandal fades and it tends to start drifting again. Meantimes, while all this drift is going on, times and technology and states of research change and standards of accountability change, and that's what leads to the dilemma. So I used as a starting place, actually, the resolution that you passed in May of 1997 that "no person in the United States should be enrolled in research without the twin protections of informed consent by an authorized person and independent review of the risks and benefits of the research." There is an interesting restatement of that, if we could go to the next one. The next day President Clinton in a commencement address made a statement that "we must never allow our citizens to unwitting guinea pigs in scientific experiments that put them at risk without their consent and full knowledge." It's kind of an interesting restatement because it focuses on "without their consent" and it talks about risk but it doesn't talk about independent review, which I think is a pretty interesting sort of twist on how these things happen.

As I thought about these two statements, but particularly your resolution, the thing that kept coming back to me as I thought about the issues of expanding Federal oversight, which is really where my charge started—with expanding Federal oversight, I couldn't ever get to the expanding part when it was go glaringly clear to me that, even in our present system, the twin protections that your resolution talks about are just not always available to human subjects. And it just was a huge stumbling block for me. Every time I got to thinking about the expansion part, I kept getting to the fact that I don't see how it's actually responsible to say, "Well, we're not doing so hot with what we're already doing, but let's expand and do more." I couldn't get there. So where I kept coming back to is looking at the shortcomings in our actual application before you get to the areas that we don't cover at all. I think we have...oh yes, the present regulations—this isn't on the list—but the present regulations, just as a reminder for people who perhaps are not as immersed as you are, is that we actually cover right now three areas of human subject research, in marked contrast to non-human animals. There are only three kinds of research that we cover—that that's funded or conducted by an agency subscribing to the Common Rule, things that are regulated by the FDA, and research that's covered by a voluntary assurance negotiated with OPRR. We know that there are a lot of problems with this system, and I just excerpted a few of them here. The OTA congressional testimony by Dr. Nishimi in 1994 talks about the current system, while though changing incrementally, has fallen short of implementing or did not implement at all recommendations made between 1973 and 1982 by an ad hoc congressional committee of the Department of Health, Education, and Welfare, a congressional report, and two congressionally mandated commissions. I actually think

this latter point is one that has serious implications for your work, because, if you are going to put in all this time and energy and effort at writing reports and making recommendations, I think it behooves you to think carefully about what are the strategies that will maximize actual implementation rather than falling into this category of recommendations that never get implemented. And I would be fairly concerned about that in your shoes. And at the end of my paper I made a specific suggestion in that I think the more specific you are in your recommendations in terms of statutory implementation, in terms of it should be this way, it should be in red ink, it should be Thursday afternoons, the better off I think you're going to be rather than saying "Think good thoughts and honor your mothers."

I pulled out one other finding from 1995 from the Advisory Committee on Human Radiation Experiment Findings, which talks about the shortcomings in current Federal agencies. In most Federal agencies current mechanisms of oversight of research involving human subjects are limited to audits for cause and reviews of paperwork requirements. These strategies do not provide a sufficient basis for assuring that the present oversight system is working satisfactorily.

So my effort resulted in the following recommendations, which I've just summarized here for you. There are really three recommendations. There's four bullets, but there's three recommendations. One is to start by focusing on correcting the identified deficiencies. I don't see credibly how you can expand the scope of regulation if we can't do our present job adequately. And furthermore, since we have so much documentation about how we're not doing it as well as we'd like to be doing. The present system has many, many strengths. The present system does many things well. But we have a plethora of documentation talking about the places it falls short. I think that's an important starting place.

Unify Federal oversight in one office or agency. I spend a fair amount of time in the paper talking about that, and I'll talk a little bit about that today. Use existing offices as a model. This comes from the pragmatism of my life, which is that I just don't think that we're likely to get enough sustained attention to invent an entire new model, so I'm saying let's take a model that exists and adapt it. And there are some interesting ones out there, I think.

And then expand regulation incrementally rather than globally. I've suggested essentially a "known risks" or "known dangers" approach. Take places that we know there are problems and use a cost-benefit model and expand and use those to expand regulations to places that we know humans face more than minimal risk and deal with those.

I told you that I really kept getting hung up on the identified deficiencies. And you know, in addition to these three that I've summarized, just looking from 1995 forward, you have the Advisory Committee on Human Radiation Experiments; you have

the General Accounting Office review; you have the HHS Inspector General reports. None of these are trivial pieces of work, and I think—you have the reports from Drs. Fletcher and McCarthy talking about some fairly significant problems in the current system. You have the interagency working group that preceded the Advisory—I mean it follows the Advisory Committee—I mean it goes back. You have the 1983 Presidential Commission, many of whose recommendations were, as best I can tell, never implemented in this area. So I think the one thing that you're going to find at root of all this is a question of resources, and that comes back again to this issue of how do issues of self-regulation arise and present themselves. And the way that they present themselves is that they're scandal-driven. And so then in the absence of an immediate and burning scandal, the resources and the energy and the attention tend to drift away, and so I think you'd better think about that structurally when you go to resolving these problems because, unless the structure is built properly, it is inevitable that, once the scandal isn't absorbing people's attention or some different scandal is absorbing people's attention, the system is going to drift again. So I think that's an important issue.

I summarized for you some of the identified deficiencies in the system—the effectiveness and IRB oversight; the Inspector General reports; the GAO reports. All of them talk about aspects of the current system, and they really focus issues on the mismatch of effort for result in a lot of cases. The message that you can take away from a lot of these studies is less paperwork, less procedure for less-than-minimal risk. Put the energy where the risks really are. But the effectiveness of IRB oversight, there have been changes in the environment that have dramatically affected it—the increase in clinical trials, multiple-site clinical trials, etc.

Inconsistency across the government. It strikes me that this is a place you can really make a difference. There is enough impetus out there that with your added weight it strikes me that this is a place that you could actually just get the problem taken care of. We're not that far off. You have the Presidential Executive Order to build on. You have your own staff work that I think is probably, when that survey is complete, will be pretty compelling proof. You have...you know, we have data from 1983, from 1991, from 1994, and your own staff work. There will be a pretty compelling case that there's really no excuse that we have 17 Federal agencies that subscribe to the Common Rule, more or less, and implement it more or less, and at least 23 or 24 Federal agencies that conduct themselves research as well as sponsor it. Hello!

The regulatory burden is again this issue that is a recurring theme in terms of trying to do a better job of matching the effort with the paperwork and the procedural burden that we put on people. There is a significant regulatory burden, I can tell you, from the institutional perspective. It's worth it in almost every case. But there are some cases where the degree of the burden is simply disproportionate to the gain and it doesn't help breed respect and credibility for the system when we ask people to put in empty work. The ACHRE report estimates that 40 to 50 percent of human subjects research

that it surveyed involved less than minimal risk to the subjects. Now I don't know if that number extrapolates, but it's sure a pretty interesting starting point for discussion in thinking about where should the regulatory burden and focus and where should our energies and really precious resources of time go, because it's the time of the investigators, of the subjects, of the review boards, of the people who have to review the review boards. Where should those resources be devoted?

Weaknesses in the present Federal structure. I think that those topics are really fairly definitively covered from the OIG report, the Fletcher, the McCarthy papers, and the GAO, all of whom talked about this structural deficiency of the location of OPRR and NIH. I understand that that's getting some attention right now. Again, it's an issue that maybe we could just solve once and for all, particularly if you weigh in on it.

Resource and commitment issues. I really think these are the major issues. I really think that this is where your weight needs to go because the glaring problem in a lot of these cases—aside from some misdevotion of resources in terms of the procedural heaviness on places that perhaps don't have a cost-benefit—but the real issue is how serious are we about protecting human subjects who are at risk? And if we're really serious about it, then we'd better think more seriously about the resources we devote to it, because giving it lip service and not providing the support, either in the Federal apparatus or in the educational support for the IRBs and for investigators—this is never going to go anywhere. And so unless this resource issue is grappled with fairly directly, I think that you're doomed for another report that sits on the shelf. And so I don't think that your work deserves that. I hope you don't feel that way. And so I hope that this resource issue will sort of front and center when you get to thinking about these issues, get very serious attention.

And then, finally, we get to the unregulated activities, which was again where I was supposed to start. I'm sorry; I just couldn't get there with all these other issues in my way. So I'm recommending that you correct the identified deficiencies, which is...and I've again sort of laid out some of the issues that recur over and over and over. Streamline the assurance system. Focus resources on areas of greatest risk. Require full adherence to the Common Rule. Unify government oversight. Assure independence of the government monitoring function. Provide adequate resources—this is a theme. And then finally, expand the regulatory scope. So the themes for the change that I've talked about in the work that I've done for you look...are really threefold I think. One is achieving consistency. We can do better. We ought to do better. I hope we're better than how we're doing right now. Unify Federal oversight. And then expand regulation incrementally.

For achieving consistency I think there are really four issues. I've zoomed past the next one and I'm on the slide that has "Achieve Consistency" at the very top. Adherence to the Common Rule, absolute minimum. Unify government oversight. Independence of the monitoring function. Adequacy of resources. These are all issues

that I've talked about. I just tried to group them under the heading of achieve consistency.

Under the heading of “Unify Federal Oversight”—this issue of reducing the burden on regulated entities to focus resources more effectively I think is a very serious one, and I think it's one where some thoughtful consideration could yield real gain without any particular cost. There are real costs in some of the things that I think you're going to need to do. But by a better balancing and better focus and better devotion of energy that already exists I think you could find significant gain. Streamlining procedures is part of that. There's been a lot of talk about streamlining procedures. OIG reports talk about reengineering the process. The GAO report talks about it. Some of the Presidential Commission issues talked about it in 1983. Improving accountability. This is again back to the issue not only of IRB effectiveness, but of how we use our own existing Federal resources. I think there probably need to be more Federal resources, but we can improve accountability if we use what we are already devoting better and thereby I think build a better case for more.

Strengthen educational efforts. I really think in a system of professional self-regulation or self-regulation of any form, the educational efforts are the absolute cornerstone. And in a system that is as full of transients as the research system is—you have graduate students, you have investigators—it calls for serious ongoing educational efforts—for the investigators, which the OIG, the ACHRE talked about, and for the IRBs themselves. There's two different categories of educational efforts required, and they're both very important. And I don't think you can substitute one for the other. I think you have to have both, because for self-regulation to work, for the whole system to work, you have to be able to tell people what are the principles upon which it rests, why is it important, and how does it apply to them, because people are always so involved with their own very important work, which is how we get useful things done in this world, is because people have a form of monomania about this really interesting, neat thing that they personally are doing, you have to be able to penetrate that enough to say, “Yoo-hoo. There's a bigger picture and it's worth your energy to pay attention to it because here are the ethical principles around which we have consensus and to which we all subscribe. Here's why it matters to you.” I personally think—and again this is a pragmatic conclusion that I came to—is that maintaining separate FDA and OPRR jurisdiction seems to me the most sensible way to go. You've got two entire separate statutory operating instructions. You have two entire constituencies. You have different goals, really. So I think pragmatically, rather than trying to go at redoing the whole thing and change the statutory authority and all those things, my recommendation would be to consider maintaining their separate jurisdiction but really putting on a lot of pressure to improve their already good working relationships and coordination. I recommend a Memorandum of Understanding that lays out more explicitly. And for example, if you look at some of the recommendations of the General Accounting Office and the HHS Inspector General, it strikes me again that there's real gain to be had in a Memorandum

of Understanding between the two that looks at, for example, who has responsibility for the effectiveness of the IRB's operation. Who has responsibility for the human subjects, as opposed to who has responsibility for the validity and efficacy of the results of the trial. So I think there's gains to be had there.

There may be other settings that you're going to need to explore where specialized provisions may be helpful. I don't know enough about it, but it strikes me that there may be similar specialized issues with, for example, things that the Centers for Disease Control does; some of the things that the Department of Energy does. I don't know enough about them, but it strikes me that those are areas that somebody needs to look at with a little bit more care.

Finally, I've said about unified Federal oversight that there are some interesting existing models, and I proposed three. And the reason that I selected these three, aside from the fact that they were the best ones I found, is that they each have an element that I think commends itself to your attention. The Office of Government Ethics distributed model is very intriguing, where they have designated Agency Ethics Officers in each Federal agency with joint reporting lines, so they achieve work with the people inside the agencies and they also achieve a consistency of policy interpretation through the educational mechanism, through the reporting mechanism, and through the connection in the networks that they build of the government ethics community. It's a very interesting model, and I think you could extend it beyond the government to include the regulated entities. It wouldn't just be an intra-government kind of function. So I think there's a lot to commend it there, and I'm very grateful to Stuart Gilman of the Office of Government Ethics, who spent a good deal of time talking with me about how they function and how they work. There's a lot here, I think, that you might look at with some care.

The Office of the Special Counsel is interesting, I think, particularly for how it works inside the government. And then the Nuclear Regulatory Commission—although the scale is sort of, the dimension that we're talking about it off the scale in terms of all these other things we're talking about. The model part of it there that I think is particularly useful for you is how it works with a commission and then the whole agency itself. There have been many observations about the fact that the United States is one of the few places that doesn't have a standing bioethics commission. Even you have a limited term. Yet another commission with a limited term. So there is no standing body. There's been a lot of conversation about that in terms of how do we deal with those issues. The Nuclear Regulatory Commission, I think, raises some issues that bear consideration for you in that arena.

I think you're going to need to commission some additional research. And again this goes back to the issue of all the reports that are sitting on the shelf out there. I think the more specific you can be, the more likely you are to make headway and not have wasted some of this effort. And so I think that you might consider commissioning some additional research. I simply don't have the expertise about the government model and

inside, working in the government in the political environment and bureaucratic environment is beyond me. But I think, to be really effective, you're going to need some really top-quality advice there.

Okay. Finally, on my last slide I'm going to tell you about the task I was actually given. It really did take me this long to get to it, and I've listed some examples on pages 23 and 24 of the paper that you have, where I've suggested some places to start for known risks, places that we know there is unregulated research or at least research over which there is no authority to investigate or assist the subjects when they complain. What we say to subjects in these cases is, "Gosh. I guess you'd better go see a lawyer." We ought to be better than this, folks. I mean, this is just not a sensible or morally appropriate environment, I don't think. And so I listed a set of examples for you. I think that there are—you know, the unapproved invasive procedures is a fairly obvious area of a clear known risk to human subjects that I think would provide a basis for saying, "There's a risk and we're going to take jurisdiction." Genetic tests. You've spent a lot of time on issues related to that. Problem reports. It strikes me that there could be developed an appropriate regulatory or statutory basis for when you can document that there are a sufficient critical mass of people at risk that the government would take jurisdiction. But I think that a cost-benefit analysis, where you document that there are problems and people who are at more than minimal risk, is the way to expand regulation, not by sort of globally doing it and then trying to back off of it.

I spend some time in the paper talking about the issues, the pragmatic issues involved. If you say, "We're going to treat humans in a corollary way to non-human animals," as the Animal Welfare Act does, immediately you run into the issue about the definition of research, which was *by design* from the original National Commission in the 1970s quite broad. I think I do have a slide there at the very end that has what the definition of research is; it's the last slide. It's also not on the handout. I thought maybe it might be useful at the last minute. It's a very broad definition, and it is intentionally broad. And I think that its durability over these decades speaks to the wisdom of the breadth of this definition. Then there are the exemption categories that were developed with much pain, and again, taking practically 10 years to develop. So one approach would be to take global jurisdiction over humans in a way corollary to animals. It is ironic that we provide more protection to some animals than to humans in this country, but there are also some reasons when you get down to it. So you could take global jurisdiction and then try to back out by building new exemption categories and things like that. I wonder if the time and effort that that entails is not ultimately more costly than taking the known cost-benefits, so documented risks and then you go forward. Because what worries me a great deal is it is just not difficult at all to envision the creation of an extensive, possibly profit-driven, rubber-stamping review system that dilutes attention to the really serious ethical issues. You could have a lot of people spending a lot of time, moving a lot of paper around. And you could have really good documentation and not much substantive ethical consideration of the really hard issues.

And so I personally think—and my recommendation to you and where I ended up after all of this sort of extended musing on your behalf—was to focus on the places that we can document that there are people at risk and focus the energies on that in several quite concentrated ways: streamline our system so that we're doing a better job of devoting the resources we have. Devote the additional resources that it takes to do the appropriate education. And then make it very plain that what we're going to protect and why are human subjects at risk. So that's a summary of what I've done for you.

DR. SHAPIRO: Thank you very, very much. I think this has been very helpful. Some of you...colleagues, questions they may have.

Professor Capron: Two questions. The first is that you recommend as an avenue for asserting jurisdiction for this broader review of research that is not now covered by the Federal regulations, an interpretation of the 1974 Research Act. And I think you are correct in suggesting that we return to legal counsel for the various departments, particularly for HHS, and ask them about that. But have you given consideration as to whether or not, as so interpreted, that statute would run into problems comparable to the problems the Federal government faced in the Grove City case, involving whether or not an institution could be forced to adjust the way it did business—I think an educational institution in that case, City College—because it took certain categories of Federal funds not related to the activity that the government was trying to have it change?

MS. GUNSALUS: I acknowledge that those problems exist. And I'm not sure that it's particularly useful to you to adhere to my own philosophical basis of "There is no free lunch." But there are some serious legal problems there. I think that HHS has some very competent folks, and I think you could get some useful advice. My instinct is, both from the perspective of the regulated and—I'm sorry, Alta, a lawyer—my instinct is that there's some room to be gained here. And, again, if there's some principled focus and it's accompanied by some streamlining of the regulatory burden, I think you could strike a reasonable middle ground.

Professor Capron: Well, that gets to the second question. When we discussed this topic—and we agreed that we were going to have papers sort of pro and con from people with a government perspective and we ended up with the Fletcher and McCarthy papers—the suggestion was made by David Cox that we commission yet a third paper, which was the one that you're doing, because David was speculating that, in fact, many people in the nongovernmentally funded research sphere would be happy to have this kind of oversight because it would give the sponsors greater assurance that the research was something that they wouldn't be embarrassed by and because many of the researchers would be happy to do it because they're also people who do governmental-sponsored research anyway. There were just any number of reasons. That I don't think comes out in the report, and I wonder whether, among the avenues that you looked at but maybe haven't fully reported on here, was any touching base with relevant industry groups, I guess when the project was originally described, which is not to criticize the

project that you did—and I actually agree with the two-thirds of the paper that you say is basically crepatory to the topic. I think you're right. We can hardly recommend imposing a system on the private sector if we can't say it's well implemented for the public sector. But do you have any avenues for giving us that information? The Pharmaceutical Manufacturers Association—did you find out what they think...?

MS. GUNSALUS: I talked to a fair number of people along the way, and the general response was in theory this sounds pretty interesting. Show me something specific and we'll react. Well, I wasn't there. I am going to throw this back to you and say I think you're going to have to refine a little more which direction you're going to go or else the response is going to be equally amorphous.

Professor Capron: Well, the way that you're talking about here, the major decision point is whether to identify particular categories of research and say they ought to be included, or the other, which is to say all research, but of course we don't really care too much about this trivial stuff. The trivial stuff supposedly already off the table because it either doesn't involve any risk to human subjects or some other reason.

MS. GUNSALUS: Well, talk to somebody in an IRB that's had to deal with the FDA. I'm not sure they all feel that way.

Professor Capron: But the FDA is already dealing with a large part of the private research entities. I guess....

MS. GUNSALUS: I'm just telling you that the regulatory burden and getting the trivial stuff of the table, I'm not sure you will find uniform acceptance out in the field that we've achieved that in any meaningful degree.

Professor Capron: It just seems to me that you're evaluating examples of things happening in a wide variety of settings—in vitro clinics, dentist's office, doctor's office, psychotherapist's office, which don't have any particular unifying aspect. I mean, they don't all involve general anesthetics, or they don't all involve surgery.

MS. GUNSALUS: No. That's why I went back to try to build some categories that I thought represented starting places for consideration. I think this issue of expanding the scope of regulation is—the more I got into it, the bigger a topic it appeared to me, which is why I came back to this issue of places you can construct a really compelling governmental interest.

Professor Capron: But your example on page 25 says, “Other research activities that could present risk to human subjects include health services research and internal evaluation research.”

MS. GUNSALUS: That was there just to illustrate the breadth of this. If you go back to all research involving humans, there are arguably some forms of journalism that would be encompassed, and new exemptions would be required, I am convinced. And

the process of developing exemptions is not a pretty process, not is it an expeditious process.

Professor Capron: But you are saying, just so that I understand your oral presentation, you are saying here that these are examples of things that a well-factored rule might encompass, might well encompass, because they involve known risks.

MS. GUNSALUS: Well, I personally think that what should happen...I mean, if I get to be king and say it's this way, I would define a fairly small number to begin with—the invasive procedures, the genetic tests. I mean, I would start there. And I would accompany that with the other reforms and show that we can do a credible and effective job and do it well and build incrementally. I wouldn't start out by encompassing very large areas that I'm not convinced we can handle credibly and effectively.

DR. LO: I want to thank you for your talk and I appreciate your urging us to think hard about the implementation of our recommendations and not to have a report that sits on the shelf and to focus on the serious problems and cost-effective revenues and intervention. I want to ask your thoughts about something that's troubled me as I've read, what, two draft reports. But I think we have tried to look at big problem areas involving—subjects who may lack decisionmaking capacity and DNA testing are two examples. One of the themes that one gets out of our recommendations is that we are calling on IRBs to take on the responsibility of exercising their discretion to add in additional safeguards, which are not strictly required by the current regulations but are consistent with them and would promote greater protection of subjects. This, in a context of numerous reports that you've documented, our concerns are these aren't doing well what they're now supposed to be doing. In fact, they're getting eaten up by too many protocols, limited resources, inadequate education, etc., etc., etc. Can you give us a candid appraisal of whether you think the approach we're taking of "let's try and ask the IRB as thoughtful local representatives who are currently charged with providing on-site oversight to do even more." Is that a sensible approach and a cost-effective approach to...?

MS. GUNSALUS: Well, I think it is a sensible approach because my experience is that there are a tremendous number of thoughtful, sincere, deeply caring people who really want to do the right thing. But in order for them to do those tasks, I think you're going to have to try to clear some of the underbrush of the places that we really do put regulatory burden and try really better to balance the resources, because there really is a finite amount of time and energy and human capital. And I think that our system of local control is inspired in many ways, and I think it has lots to recommend it. But if we—and I think that that's exactly the sort of issue that you want people to grapple with. But if they're busy looking at subsection 9/4.e, subparagraph 4, and not thinking about...you know, what do you really want them to do? Do you want them to give the thoughtful ethical consideration? I think so. Is there a better way to balance getting some of the

other stuff done and is there some of the stuff that we're doing that doesn't need to be done?

DR. SHAPIRO: Thank you, Jim, Larry, and Eric.

DR. CHILDRESS: Thanks very much for that clear and helpful presentation, although I want to press you a bit on exactly why you feel we should not try to extend the system that you do concede has many positive features and virtues. It's broad...

MS. GUNSALUS: I'm not here to knock the system in general.

DR. CHILDRESS: So why shouldn't we extend that as broadly and comprehensively as possible? And I heard at least three different sorts of things, and let me just press you and see where you stand all over. What really is the critical thing for you? You say, and you said particularly at the beginning, that the system is too flawed as it stands to extend as broadly as we might be thinking about. But it seems to me, if that's the case, that would also be an argument for not extending it incrementally. That it's an argument for not extending it at all at this point; to fix it. Then you might have a second argument—and it seemed to me this was present—that we shouldn't even have tried to extend it globally because we couldn't do it, it wouldn't be the political will and opportunity to do so. And then a third one would be that, even if we could do it, it simply wouldn't be worth the investment of resources required to have it as globally as we might want it to be.

MS. GUNSALUS: Could I choose "D"?

DR. CHILDRESS: I'm just sort of interested in where you finally stand...?

MS. GUNSALUS: The fundamental reason is I don't think you should extend it globally because I don't think it will work. I mean, that's the bottom line. And then if I can go back and choose "A," which is—I think what I said in the paper, and I may not have been as clear today as I tried to be in the paper—is that yes, I believe that some expansion is warranted. But I don't think you get to that step until you correct the identified deficiencies first. I think it's a prerequisite. Now, I think we need to get to the expansion, but I don't think that there's a good, strong ground to stand on for getting there until, in a very clear-sighted way, some of these issues are acknowledged and addressed.

DR. CHILDRESS: I guess that's where I have the problem is. I think there's many positive features, as you've emphasized.

MS. GUNSALUS: I think there are.

DR. CHILDRESS: Then I'm not sure why we shouldn't go ahead and extend those. That is, I'm not sure we have to correct all the flaws in the system. If there are some really positive features that might well...

MS. GUNSALUS:...because I think that more will break it. I think it's the straw that breaks the camel's back. I mean, I think that there is...you know, I have seen IRBs do really magnificent things. I mean, they are neat. The discussions that happen when you get to what you really want the IRB to do are really very impressive and inspiring. How often do IRBs get to have those discussions? And then you're going to add more? I just don't think it'll work. Now, I offer it for your use and of whatever use it is to you. You may, in your collective wisdom and your work, come to a completely different conclusion. That's okay with me.

DR. MIIKE: Let me get it straight first. You want a more focused system than currently is, but then you want to expand it broadly?

MS. GUNSALUS: I want to expand it in targeted, focused ways. Yes.

DR. MIIKE: No, what I mean is to the areas where it's not being used now. Isn't it more a question, though, of the mechanism that we use, because when you set up a formalized process, you must have rules. And I think I could argue that, conceptually, the way that all the things that we've discussed now is supposed to provide IRBs where it's going to be implemented in the system. A method of filtering out the unimportant from the important. And I think that what you're saying is that they're not doing a very good job of that, that they're erring on the side of caution, so they want to review everything.

MS. GUNSALUS: I don't think we've let them do a very good job of that because of some of the regulatory burden.

DR. MIIKE: Okay. But what I'm saying is that if I look in what is in the administrative rules—and the legalese aside—it's not a question of saying you'd better review everything. It's saying, "Here are some ways in which to filter out the things that you don't really have to pay attention to, and here are the areas that you really should. So is it—what is wrong with the system? If the way that you're saying is to just focus on some immediate issues. Don't we also then face the problem with, it's your idea of what is an immediate issue, it's your idea what's a great harm, it's your idea of arbitrarily picking out all of the kinds of experiments that go on. And so how do we get to the point at the beginning?"

MS. GUNSALUS: I would refer you to—I think you could spend a pretty instructive couple of hours reading the Presidential Commission's Report from 1983; the Advisory Committee on Human Radiation Report, particularly chapters 17 and 18, that focus on the flaws with IRBs as they function; the OIG Executive Summary Report, the one that's called "Institutional Review Boards, a Time for Reform: The Executive Summary." I think that that would give you a really pretty focused picture. I mean, it talks about streamlining the assurance system, which is a very low-cost, very immediate, I think, very high-gain reform you could make tomorrow afternoon. Okay. Government time. Six months from now. But there are, in those reports, there are enough quite

explicit, well-based, well documented examples of places that we've just put the *emphasis* on the wrong syllable. I don't know if the transcript will pick that up.

DR. CASSELL: I also want to thank you for your presentation, but one aspect of it I think is important to remember, and that's the pragmatic business of what will in fact make what we want to happen happen? I agree that the IRBs are burdened with regulatory stuff that they don't have to amongst the less-than-minimal-risk proposals that they go back over and over again, send back out to the investigators so that they can come back to them and so forth, in part because that's what the regulations call for, and in part because you can't underestimate humans' desire to evade responsibility, big stuff. And I would think that one of the things that we could do that would have a big impact, because it would make a grateful nation of IRB members, would be to recommend the cutting way, way back of that kind of burden. I mean, in concrete terms, at the same time as we offered the educational opportunities which you stressed and which we've talked about here at some length, and that the doing of that would gain us some fans in the IRB system at the same time as you suggest a change in the overarching regulation. I think that those three things alone might be doable. And then we have the issue of extending because we've got people's attention and we're the "nice guys." And that always helps.

MS. GUNSALUS: And effective. It's nice to be effective while you're nice, too. I mean, I really like nice people but I prefer my nice people to be competent and effective at the same time.

DR. CASSELL: If I do something nice, most people think it's effective, and so...

MS. GUNSALUS: I'll take you up on that some time.

DR. CASSELL: So I think that stress on those in your comments is proper and would be very helpful.

MS. GUNSALUS: Did I leave out the GAO report, by the way, the General Accounting Office Report? Okay. Good. I didn't mean to.

MS. CHARO: I'd like to turn to a very pragmatic issue...

MS. GUNSALUS: Oh, my favorite.

MS. CHARO:...from your paper which, by the way, was wonderful. It went far beyond the presentation in terms of detail and scope. Your very strong call there and here for NBAC to take up this issue with a high attention to detail and specificity. You've mentioned it several times. Now, since at first blush, some of the crucial considerations are going to be things that have to deal with peculiarly governmental concerns—scope of authority of various agencies, the realistic mix of respective certain agencies to take on additional duties or to receive congressional support over the years, and such. I find myself wondering if the reason you're making this recommendation to us is because we think that this group of people constituted with these purposes in our

charter has some peculiar expertise that we can bring to bear on the question of how to implement the ethical commandments that I think you're leaning us toward. Or whether it's simply out of desperate frustration at years of there being no action on previous reports, you simply turn to this body and say, "Take a shot at it."

MS. GUNSALUS: Could I answer your question "Yes"?

MS. GUNSALUS: I think that you have a lot to offer. Not only do you have your collective expertise and wisdom, you have the moment and you have the resources. I say, "Capitalize on it."

MS. CHARO: You answered my question.

MS. LEVINSON: This morning I was concerned with some of the discussion about being reluctant to attempt to rewrite the regulation, to change the rules in a dramatic way. And I think that that was a laudable attempt to be pragmatic, to think about the concerns that will be attached to a major change in regulations. Having said that, I would like to encourage you to take this recommendation that Tina's made to think about, to think outside the envelope, to think about where the deficiencies are that was your charge in the Executive Order to consider and advise and make recommendations on the accuracy of the current system. If the system isn't adequate, point to that and be specific. I don't think that you necessarily need to think about as pragmatic concerns as the statutory authorities. That's the sort of thing that the regulatory agencies are going to have to consider and you don't. But if you identify the principles and the inadequacies in the current system in addressing those, I think Bernie made a point earlier in considering the capacity report about his discomfort in recommending additional roles for the IRBs when it's already evident that they're overstressed and overburdened. If you focus on that and say that they can't possibly take on more, which you would like to recommend, unless the streamlining or other deficiencies are addressed first, I think that that can be heard and implemented.

DR. SHAPIRO: I have a comment. I think it's relevant, I hope it's relevant, to the discussion we're having here. I have some other questions as well. But probably the single phrase you've heard most often here now over the last two years is overstressed IRBs. Somehow that comes up in every venue and every problem and so on, and I really have to say that at some important level I don't understand that. I understand that some people think they're working too hard. I understand that issue. But it's either because IRBs are doing work they don't need to do—just one of the things you suggested—that is, there's some low-risk material or some totally unnecessary paperwork, and so that we have imposed burdens on them which have no dividends to anybody. And that I understand is a possibility, that maybe we have aspects of the system just completely unproductive of anything that we care about. And if that's true, of course, we ought to streamline them. I guess that's what you meant by streamlining.

MS. GUNSALUS: It's one of the aspects.

DR. SHAPIRO: One of the aspects of streamlining. But then—and of course I think we can all agree—to the extent that those dividends are available, we ought to grab them and bank them for some better purpose. I don't think this really gets to be a real benefit. But then there's the other tension, which has always bothered me, that is overstressed IRBs versus protections we really want. And I don't want us to get...that's a dangerous territory to be skating on. And so—I mean, I'd rather the solution to that, if you have attention there, to appoint another IRB. Instead of having one, you'd have two; if you're going to have two, you can have three. And you worry about their education and so on. But I want us—my own view is I want to be very careful. We do want to eliminate the unproductive work we have.

MS. GUNSALUS: I think there's three things in what you've said that it really might be a help to pull them out separately. One is making sure that the IRBs have the tools to do what we really care that they do, and that's partially an educational function; it's partially a guidance function; it's partially what we assign them to do. One is the point that you bring up, which is how many IRBs do you have? I participated in a site visit with OPRR once at an IRB that, when the entire group was assembled because they were all there for this official function because OPRR was site-visiting them, there must have been 23 or 25 people around the room. And you looked at their agendas and you looked at what they had done, and GAO and that OIG report both point out that if you divide the number of protocols by the amount of time allotted to the meeting, how much time did they give each one? Well, 94.6 seconds. Twenty-three people in the room—it might easily been a much more productive approach to have two 11- or 12-person IRBs than one 23-person IRB, where they all sat and looked at it. And there are many institutions that are doing very neat things with having specialized—you know, a dental IRB, where you actually focus in so that you focus the expertise and do some interesting things. You know. So the tools.... But there's also the issue of collective wisdom. There's a level to which every IRB, I think, has to grapple and build a group sort of personality and go through some of the fundamental ethical issues for itself. I mean, some of this you only do by hands-on grappling with it. But there's also—and I believe that it's in the outline that you're not discussing now because I'm talking—is this issue of maintaining some kind of repository or central place. We are very short—I mean, one of the things that has struck me since I've been in this “train wreck” business is how poorly we as institutions share our expertise and hard-earned wisdom with each other. I mean, we really do a crummy job of learning from each other's mistakes. And I've become fairly cynical about our ability actually, really to learn from each other's mistakes, but we could sure make some efforts at sharing information and sharing decisions or at least here's a list of things that we found it really effective to talk about when we have a case of this nature. So that the IRB doesn't have to come up with that list as well as work through them. So there's some economy of scale that we could achieve if we just configured ourselves a little bit differently in several dimensions.

DR. SHAPIRO: I just want to be...I mean, those are very helpful remarks. I just want to be careful that we don't define a zero-sum gain for ourselves that puts us in a box we can't tolerate, because there are all kinds of tradeoffs in the margin between these activities and these other activities, all the kinds of things that go on in these various organizations. I'm not going to focus all the costs on just protections we think are important or some of the costs, not all of them.

MS. GUNSALUS: I think we're talking about more at several levels. And my only plea is let's really make it an effective use of more. I think that there are compelling arguments for more, and I believe that we ought to have more. But I sure wouldn't want to see it wasted because I think that undermines the argument.

DR. SHAPIRO: Although the institution of accreditation has both good names and bad names—beloved and hated—they're all kinds of controversy in that area which I don't want to discuss. I was just wondering whether that model or some transformation of it, where there would be in some sense peer review of systems is something you gave any thought to at all as you went through this. It's something that might work. It's a way of sharing information; that's all. It's one of the things—is that something you've thought about or...?

MS. GUNSALUS: I didn't think about it much more than to reflect as I read the General Accounting Office report and the Office of Inspector General report, where they talked about looking at IRBs' effectiveness and auditing the functioning rather than the output. I think there were some pretty interesting ideas there, and the report about interesting approaches—I mean, here's this OIG report that went out and collected innovative, useful, helpful, neat things that IRBs are doing to improve their functioning. What can we do to propagate that? So beyond the concept of reading their reports and thinking, "Boy, this is pretty interesting and somebody ought to think about this more," no.

Let me ask one final question. There are—I can't think of any close analogies—but there are other situations in society at large where there are risks, where people are exposed to different kinds of risk. Let's say for a corporation, it's financial risks; and they have auditing procedures, which distinguish precisely this. They try to focus on the risky areas and just let the other stuff go by in some sense and at least have a much smaller level of scrutiny. And there must be many other entities like that which I'm not really familiar with.

MS. GUNSALUS: Well, handling conflict of interest inside academic institutions is, if you look at the way that we do it, it's functionally a risk-management model. You know, we try to identify what we think the risks to our missions are; the risks to teaching; the risks to research; the risks to service; the risks to public credibility. We try to identify what they are. We try to assess what are the circumstances that the risks to the missions arise. And then we try to focus our energies on those rather than...and

define out things. You know, our rules say we're not really very interested in activities that you would report on in a promotion and tenure dossier. If there are things that we are going to assess you on, scholarly activities that we're going to assess you on, within parameters, those don't concern us. Here's the universe that concerns us. So there are a lot of risk-management models out there that are already in use.

DR. SHAPIRO: And my question was whether you had identified any that you think might be especially appropriate here or just asking us, which is perfectly fine, to try to look at that model and see what we can discover.

MS. GUNSALUS: That's why I tried to focus on what are the principles and what do we really care about here? And that's actually how I got to know identified, documented risks to real human beings that we can look in the files and say, "Here's a human being who was hurt because..., here's a human being who was...." And this was a human being who had no recourse. And surely we're better than that.

DR. SHAPIRO: Okay. Well, thank you very much. Well, thank you very much for being here and sharing your paper. I'm sure we'll have more conversations about this as we go ahead with this particular project.

MS. GUNSALUS: May I just add my thanks to the incredible value that Eric Meslin added to this paper through his iterations with me, and I'm very grateful.

COMMENT: Thank you for mentioning that; Eric, thank you for your assistance. Let's now go back to what is now the last item on our agenda today, and that is to hear briefly from Alta and Kathi on some plans they have for a project that's upcoming this year. Alta?

HUMAN SUBJECTS PROJECT RESEARCH PLAN

MS. CHARO: Let me just reiterate the thanks because I think that set us up really nicely as well as having you've done an awful lot of the work that'll be necessary to fill out this outline. What was handed out to you today was a proposed...it's a memorandum from Kathi and me dated the 16th with an outline that looks like this, entitled "Human Subjects Protection Comprehensive Project," which can be found at your seats. If not, there are extra copies back by the staff. I want to emphasize that this is absolutely a proposed outline, and the purpose of discussing it here is to begin to discuss the scope of this particular task as well as the details on the outline. So let me just take a couple of moments to share with you some of the discussions that have been going around within the staff on this.

If you look at the reports we've issued or are issuing so far, you begin to see some thematic concerns. The difficulty of suggesting regulatory change, knowing how slow the process is in part because of the diffusion of authority, which comes up in the context of the human biological materials report—but concern about the capacity of IRBs to implement a complex set of special protections that is raised in the course of

discussing the capacity report. The dilemma posed by the knowledge that most activities will take place in the private sector, probably beyond the scope of current regulatory authority—that came up in the context of cloning. And the lack of consistency across the Federal government and Federal agency report. It's probably time to take these observations and put them together into something more comprehensive. What has been discussed so far has been something that would be a little different from the kinds of papers we've been working on, which tend to be enormous tomes that are encyclopedic in their recitations of history and empirical data, as well as being very specific, to the point of being new regulatory language, in their recommendations. What's been discussed so far is something much more on the order of a white paper—something very short, very pithy, not aimed to be at the regulatory level, something that's more at the level of a challenge to both lawmakers and regulators to find a way through statutory change and regulatory change, to implement suggestions that grow out of a fundamentally ethical set of concerns and resolutions having to do with the quality of protection that human subjects ought to enjoy, and the universe of people who ought to enjoy their protection. And I'll simply reiterate very quickly that the resources we have in hand to do this, by the way of background, are substantial. Both the Presidential and National Commission reports, the excellent Gunsalus paper, the Fletcher, McCarthy, the McKay study, and a GAO 1996 study. I hear rumors there might be more interest by GAO now again in the topic. The NIH activities currently with regard to the placement of OPRR, which may wind up as early as December of 1998. And so this outline reflects that discussion of something that's in that white paper context. Its scope, as discussed so far, is something closer to what Rachel was describing than what Ms. Gunsalus was describing, because it would be quite specific about the problems that need to be addressed. It would outline the possible solutions and some of their big advantages and disadvantages but, as currently discussed, would not purport to decide that the new system should be something that is like the Office of Government Ethics or that is like the NRC or that is located in Justice or HHS, but would simply point out the strengths and weaknesses. And we would be able to use our power to ask for an appropriate response from the appropriate agency every 6 months to see whether or not what is coming back at us meets the concerns that have been identified. So I would be very interested in hearing your reaction both to the kind of conceptualization of the project as well as to the outline.

One last thing...the timeline for this. The idea was to have some kind of draft late this spring, and so that is intimately related to the scope of the endeavor. The larger the scope, the longer the timeline.

DR. SHAPIRO: Let's see what few little questions there are. Larry?

DR. MIKE: To summarize here, instead of a prescriptive approach, we want to have a suggestive approach, and the main reason is that we work real slow.

MS. CHARO: And people call me blunt, Larry. No. Actually not. As the discussion developed, it was about whether we as a body are really the best people to make decisions about fundamentally political matters, like where in the government something is going to be located or whether our expertise is stronger in simply saying, “This is the level of protection that people are entitled to. These are the people that are entitled to it. These are the identified obstacles to achieving that that we’ve come to understand from long, hard experience with the current system. Here’s our assessment at first blush of which of the major options out there—accreditation, certification, testing PIs, changing the office’s location. Here’s our best assessment of which of those would actually answer these problems in a way that we find that to be satisfying. Please come back to us with a plan of action on how you’re going to actually do it.”

DR. MIKE: Just a thought off the top of my head. At this very moment, I think I would lean toward the prescriptive report; at least from our side talk about the pros and cons of the complements of that prescriptive report. Then we would have something concrete out there for people to react to. I’m worried about what Ms. Gunsalus had mentioned. We may just have another in a series of reports that really just, the latest report and you don’t really have much of anything.

DR. CHILDRESS: I like this outline, but there’s something that may be missing and perhaps there are thoughts to put it somewhere else, perhaps a separate document, and that’s the Federal agency survey, because at one point we had talked about—and I’m not sure. Maybe I’m missing it here. It seems to me this is...if this is item 7, this little section here, the national Federal survey, then the reports would be a lot more than a little white paper, right? Because even the material circulated in a Federal agency survey, while it’s relatively brief, would still constitute a pretty huge Section 7 in your report. So I guess what sorts of thoughts you had about that?

MS. CHARO: I think that’s a full Commission decision about how to handle this. My understanding had been that the Federal agency’s report is moving along separately and that we would simply draw lessons from it for this particular item in the outline. But how that agency report is handled and whether it’s incorporated completely or issued separately is a full Commission decision, or full staff decision.

Professor Capron: A couple of responses on the linkage of this to other projects. One has already been raised, which is the agency report. Another one is how this relates to any reexamination of the principles, the “Belmont Revisited” aspect of the Commission’s work. Point I.A. says “the origins of the justification for protection.” I wasn’t sure if that was a typo and it meant the origins *and* the justification for, or if we were interested in the origins *of* the justifications, meaning the history of use. It wasn’t clear to me. But certainly part of the way of looking at a document of principle, like Belmont, is that it provides the justification for human subjects research by explaining principles that ought to guide such research. And if so, then, as to the Federal agency thing, does this relate to anything dealing with Belmont?

The second comment is that one of the criticisms that has been raised about the IRB system, which is still where the rubber meets the road in all of these, is the question of resources for the IRBs. And I'm not sure whether the McKay report, the Inspector General, the General Accounting Office, or any of the others really talk about how much money is spent now on this activity. How does the amount that is spent compare with the amount that is spent on the underlying activity of research? Again, whether you take the prescriptive Miike approach or the commentary, "get back to us on how you're going to handle this," Charo approach, it would be helpful, it seems to me, to give some sense of what we're talking about so that people would have a way of saying, well, it turns out that we spent so many hundreds of billions of dollars on the research and a trillion dollars on health care or whatever and we spend \$2.5 million running the Federal side of the oversight and institutions themselves spend in kind another \$15 million, or \$50 million, or whatever the number is. And if our view is that doesn't do the job, what would be involved with doing the job? How much greater educational effort? How much greater staffing so that the idea of monitoring consent, getting reports on an annual basis and actually having someone read them as to what's the experience of the researcher, all the things that are in the regulations that these reports say aren't being met. Give the readers some handle on that because it seems to me one recommendation for your III.B, "Changing the Federal System for Protections," would be better funding. Some kind of a percentage of the research budget ought to be taxed to go to support the oversight function. I mean, that wouldn't be unusual, whether it's a private researcher or an NIH sponsor. So I hope that, even in a slim report, we can give the reader some sense of the magnitude.

DR. SHAPIRO: Hold on a second. I think the resource issue is really quite important, even if it's too difficult to get a comprehensive number—what do we spend nationally—the scenario, I think sampling really works and we could learn a lot from the Belmont moment and...

Professor Capron: I suspect that a lot of this is not well monetized by the institutions involved, but you could talk about levels of effort.

DR. SHAPIRO: Levels of effort, hours spent, and so on. In any case, Eric?

Professor Capron: Did I get an answer on the first question, which is what's the conceptual linkage between this and Belmont?

MS. CHARO: It incorporates the stuff going on with Belmont in that first item. That was the intent.

Professor Capron: Well, again, I guess I'm a little bit with Jim in that, although our thoughts about Belmont was not perhaps it would be as thick as the Federal agency report, which will have to have lots of data and reports in it, we did think it might take a good deal of effort and time on the part of the Commission to come up with a refined statement of the principles circa 1999.

MS. CHARO: As far as I know, the only thing that's been scheduled so far for Belmont is the conference that will take place in April in Charlottesville, and I certainly hope that some take-home lessons or insights from that meeting could be incorporated into this. I had not had discussions with anybody that envisioned this as a substitute or anything else that people might want to do with the work done at that meeting.

DR. SHAPIRO: Let me say a word about that. Obviously we all hope that the conference that will take place at the University of Virginia will be very helpful on a lot of these issues. It is not a Commission activity. It is not being financed by the Commission; it's not Commission staff that's going to take care of it and so on. But I obviously hope it will be relevant for what we do because I interpreted the discussion we had last time as this is not being a high enough priority for us to take our staff and resources and devote to that. So, yes, I hope it will have an impact. We'll wait and see. But it's not a Commission activity.

DR. CASSELL: After listening to all these comments and Dr. Gunsalus's, by the time this comes out we'll have been in operation almost 3 years, and it seems a reasonable thing at that point, like the French meal, a "coup de cognac" to help you digest what's gone on before, to come out with a short—although as you all talk it's getting longer and longer—a short prescriptive statement about what we have learned and what we think is necessary to move ahead, including changes in the IRB system, in the regulatory structure and so forth, and also what subjects, deriving from the past and going on, what subjects need to be addressed in the larger sense as we go forward. But *short*, because otherwise it won't do its job. It ought to come out there and say, "Here's an experienced body that's telling you what, on the basis of their experience, we ought to do now," as they then move forward with their larger task.

DR. LO: Alta and Kathi, I want to thank you for a very thoughtful outline. I wanted to pick up on some of the themes our guest speaker encouraged us to think about, the implementation of the report. I'd like us to think strategically or tactically about it. What is it about this report that's going to make people sit up, listen, and act as compared to all the other reports that are lining my bookshelf at home? And I think if we can think about that as we're planning, it would be very important. Because it would be nice to have an impact, and yet it's not clear to me what we're doing other than just being very thoughtful and well organized, and persuasive, which probably is going to be enough.

DR. GREIDER: I liked Alta's earlier characterization of a lot of the way that the system is currently based, as being investigator self-referral, that the whole system kind of keys into that. And the one thing that I don't see listed, at least not explicitly under weaknesses, is the fact that the system is investigator self-referral and most investigators really don't know much about this.

DR. HANNA: I just wanted to mention two things. First is I think there's a compromise between Alta's approach and Larry's approach and whether the report will be prescriptive or not. And I think we will probably know after a period of time certain areas where I would imagine the Commission can feel it can be quite prescriptive. And I think probably it would be a good idea to be prescriptive in those areas where there's great confidence. There might very well be some areas where it's not clear or the statutory language or the enabling legislation is so complex and it really needs to be worked out by regulators and rulemakers, that in those cases the Commission might defer the details to somebody else and not be as prescriptive.

MALE VOICE: Kathi just says, with the OTL alumni among us, I think the model that we could use is a fairly comprehensive report but focused case studies that say in these areas we can offer specific decisions and recommendations, which we should do.

DR. HANNA: The other point I wanted to make—I'm glad the issue came up about whether we were getting input, either through Tim's routine as paper or in other ways, from the private sector or whatever. And I think we're beginning to talk on staff about possibly convening a one-day panel meeting that would not be a full Commission meeting, where you're also dealing with a lot of other issues. But more of a hearing format where we might have panels to talk to staff, and whatever Commissioners are able to attend. Maybe a panel of people who represent a point of view from the private sector, perhaps from professional, medical, scientific societies. We need to hear from those groups about what problems they have with the system, and I don't think we've really given them the opportunity to present their case from the investigator's side. So I think there are a lot—everyone's correct. There are a lot of data out there and there are a lot of reports already, and I think it would be a good idea for the Commission to hear from some primary sources some perspectives that help us put all of that data in perspective. Because some of these reports are in direct conflict with each other.

DR. SHAPIRO: Thank you. Other comments, questions. I think that this report—we don't know what its form is quite yet, so I think these comments have been fairly helpful. We'll have to think this through again, but I think, coming out at the end of the tunnel with a report that Eric characterized and Alta characterized partly also, which reflects our best judgment about the significant things that need to be attended to, is really quite important at this stage. And whether that's an executive summary of some bigger report or accompanying the large report in some other aspect is an open issue.

Professor Capron: Two questions. I realize this is a proposed draft outline, as Carol pointed out. It sounds very tentative. I'm not urging you to change something that's great and in stone, but under the possibilities of major change, in light of what Tina was saying, just a good sense, it seems to me one might want to switch A and B because the reform of the Federal system would be the first step. And then under what is now A to differentiate, if what that standing scope protection means to research that is

not now encompassed under federally funded or federally regulated—that's what it means. It ought to be clear because one could just....

DR. MESLIN: Just very quickly. It wasn't already obvious from the authors of the memo, we have determined that Kathi Hanna will be the project director for this. We're grateful that she's able to be on staff now on virtually a full-time basis, and this is going to be something that will be her primary responsibility. And with Alta's helpful Commissioner leadership, we hope to bring this very quickly to a close. Having said that, I don't want to leave Commissioners with the misunderstanding regarding what we had talked about as early as our January meeting in Los Angeles, which was that the several commissioned papers that we have made available to us, the survey of Federal agencies, and, if you will, the residue of the several IRB reports that have been made available, would not be included in this. They are intended to be included in some way, shape, or form, that the proposal that is before you is a systematic one that hopes to get an answer that could be presented to the National Science and Technology Council as NBAC's considered judgment. So we are not talking about a proposal that replaces the combination of those three things, but how to use them most effectively. They need not be included within the covers. They are part of a volume of commissioned papers and additional materials. The proposal and a shorter than the 160- or 230-page documents that we have here before us is still consistent with Alta's proposal.

Professor Capron: But even those documents themselves have appendices probably published in separate volumes.

DR. SHAPIRO: Any other comments or questions this afternoon? Okay. It's time to move to adjournment since it's just about 5 o'clock, exactly 5 o'clock. Let me remind Commissioners that we'll try to start as early as 8 o'clock tomorrow morning. We will turn first to the Chapter 5 of the biologic materials report and try to at least go through that. Hopefully we can do that in a half-hour or forty-five minutes. We'll have to see. We should also bring the Commissioners up to date and make sure you understand where we are in a variety of projects that don't happen to be on our agenda today. We want to do that, and then we'll turn to the capacity report, which will take up most of our day tomorrow. Again, I want to apologize in advance to the Commissioners that I will have to leave early tomorrow afternoon, but Jim will be here for that part of the session. Thank you very much.

DAY TWO: Thursday, September 17, 1998**WELCOME AND OVERVIEW OF AGENDA**

DR. SHAPIRO: Thank you, colleagues, for assembling a little bit early today. Let me review what I hope will be the progress of our agenda. We're going to spend thirty minutes, no more than thirty minutes even if I have to stop someone in mid-sentence, dealing with some of the remaining parts of Chapter 5 since we don't have time to go through all aspects of it, and I'm going to suggest one particular aspect that we might want to have some discussion on in a moment. We'll then have a probably five-minute update from Eric regarding other projects and their current status at the Commission. Then we will take a short break and come back and begin what will be a fairly long set of sessions on our capacity report. I will ask Jim to chair that part of the meeting and, of course, especially that part later this afternoon when I may have to leave before we finish.

**DISCUSSION CONTINUES ON THE USE
OF HUMAN BIOLOGICAL MATERIALS IN RESEARCH**

So let's begin by going to Chapter 5 again. There is a section in Chapter 5 which we have much discussed in one way and not at all discussed in another way. That has to do with how—it begins on page 211 one way or another and goes to 213, and then a special case of that over on 215—dealing with the interests of groups you might say, people other than the research subjects themselves, and what responsibilities, if any, we wish IRBs and/or others to take on in this respect.

We have discussed it in many different ways but we haven't really focused on what we believe we really want to introduce into the various considerations that we are accumulating here, the interests of those who are not directly a party to the investigation as the investigators and the research subjects themselves. Alta mentioned something about this yesterday in one of the comments that you made, and, of course, it has come up many times. Kathi has produced some language here, including some proposed things for us to think about, and I think we should start addressing that issue.

One possibility, and I'm not recommending it actually but it's a possibility, is just to say that we ought not to worry about this, this is somebody else's concern. Another possibility, obviously, the other end of that spectrum, that it is a deep concern which needs to be taken into account just like the concerns with respect to individual research subjects. So, I could ask Commissioners to address themselves either to the particular suggestions that are made here, or to the issue in general.

I'm sorry we're going to quit this discussion, completed or not, at 8:45. At that time, we will go on to something else, but the next step in the work of the Commission in this area will be to produce a brand new draft of this report. I would, myself, hope within about six weeks to have a report that may not be finished, we may not have resolved all of the issues, but would be in good enough shape for us to send out for public comments, reactions, and so on, even though there might be some unresolved issues still at that time.

So let me open the floor for discussion of these issues.

Bernie?

DR. LO: I would urge us to try and say something about this, if only to call attention to it as a problem. I think that this is one of the areas where DNA-based genetic research on samples is different, may be different from other types of research in stored samples. I think to say that we recommend that investigators think about it but not want to yet try and write binding regulations, I think, is a good approach.

On the one hand, I think we need to just find out more information. What are the kinds of problems that we not be able to think about now but we'll only learn about if investigators and IRBs focus their attention and consider it?

And secondly, I think we want to try and get people to do more than just the bare minimum. To me, the regulations are a floor that you have to do it, but it's kind of the minimal decent things that you should do. And what we really say here, it seems to me, is think hard about things that you don't have to, we're not making you do, but it would be good to do because that's most likely where we're going to find out about potential serious problems that now we can't even envisage or contemplate.

So I'd like the language of recommending making it not binding on every case, but what's binding is you have to think about it and not that you have to respond to a certain new set of regulations.

DR. SHAPIRO: Alex, then Eric.

Professor Capron: I think I agree, basically, with Bernie's thrust. If we do that, we have to be careful then in the boldfaced language on page 212 not to describe these concerns as requirements, which is what we do now.

And I also want some help from whoever on point C, which says "Consider the implications of disseminating research results where such results may identify individuals at risk of harm who are not the subjects per se of the research." That's, to me, very okay. Consider the implications of disseminating the research results, does that mean having gotten the results, you ought not to publish them? Does it mean risk of harm to those who are not the subjects per se of research if they are an identifiable group but not otherwise? If one of the implications is that not any particular group but the population

at-large, a certain percentage of people carry a particular marker for a type of cancer—breast cancer, but not among Ashkenazi Jews, but just among women generally, or women who had uncles who had prostate cancer, or some such thing, those people are now potentially at risk. It's just very unclear. It's mushy what this means.

So I think if I were a researcher reading this, I just wouldn't know what I'd been told to do.

DR. SHAPIRO: I'm glad you focused on C. I'm also sympathetic to the kind of position Bernie laid out. If I look at the boldfaced material here at the bottom, I don't like C at all. If I understand it, I don't like it. And in some sense, I don't understand it. So I don't like C at all. I think that's rather dangerous territory actually.

The material that follows C, on the next page, begins to look more like requirements, because not only are you asking the investigator to do something, you're asking the IRB to assess whether the investigator has considered this. And it begins to feel a little on the oppressive side to me. That's just my own reaction.

Professor Capron: The latter part of it, whether the risks and benefits are an appropriate ratio, is not an new assignment for IRBs. But what is potentially over the line in that assignment is that information developed will be harmful. Now, thinking back, it's not just DNA studies, Bernie, thinking back to the early days of the AIDS crisis, when Haitians were a focus of concern, people were saying this is a disease that seems to occur among gays and Haitians and then maybe drug users were beginning to be brought in, and the suggestion was, well, are Haitians a distinct group because of something about Haitians, or are they all gay or drug users? But they were painted with a very broad brush, and particularly in New York City, I know there was a great deal of concern for that community being singled out. Now it turned out there was nothing unique about Haitians at all I gather, except there was a certain amount of the disease in the country and so the prevalence was higher there or something.

But I don't know what this advice in that context would have been. If someone had been using live people or stored tissue samples, would it have been that research shouldn't have been done which would have mentioned a group? What would an IRB do in terms of risk? There is a risk of stigma from those results. So I want to reinforce agreement with you.

DR. SHAPIRO: Okay. I have a lot of people who want to speak.

Eric. Alta, you're on the list.

DR. CASSELL: I agree that we have to somehow get this to come out in the investigator's presentation to the IRB. But asking investigators to think about something may not be the best way because it doesn't produce anything hard. But I think that it is possible to come out with the equivalent of an impact statement, like an environmental impact statement, which specifies what you believe would be the possible impact on

groups other than the source of the tissue and specifying specific terms. It doesn't have to come out. It can be laid out in such a way that the IRB can review it and then if they feel further action is necessary, let them take that action. But this would require the investigator to not only think about it, but write it down in its broadest form.

DR. SHAPIRO: Bernie?

DR. LO: I just wanted to say that with C, I agree that the language here is kind of hard to understand. I thought this actually referred to the starting point, this was the issue of publishing a pedigree, which identified specific individuals, not because they were members of the group but the person who is placed in the pedigree, you could infer from the design of have or to not have a certain genotype.

DR. SHAPIRO: Is that what you had thought, Kathi? Because that's not how I read it.

DR. HANNA: I think that was the intent.

DR. SHAPIRO: I see. I didn't read it that way at all. I'm sorry.

Steve.

MR. HOLTZMAN: I think the point there, I don't have the exact language, but you can write it to say that if you can publish in a scientifically valid way, publish the results in such a way to shield the identification. And we do this all the time, right.

DR. SHAPIRO: I understand that quite well. I agree with that. I just didn't read C that way at all. I misunderstood. I apologize for that.

Okay. Alta.

MS. CHARO: Again, I'm going to rely heavily on the lunch conversation I had with Karen Rothenberg yesterday at lunch just for the sake of the record.

DR. SHAPIRO: You didn't have lunch twice, Alta?

MS. CHARO: No. Dinner was fun though. It seems to me that there are two parts to this question. The first is how is an IRB or some other body supposed to interact with an investigator on this topic, at what points in the decision process and with what degree of authority. And the second is what are they supposed to be doing.

Starting with the "what," it seems like it might be appropriate for us to make a suggested list of IRB kind of bag of tricks that we would suggest that they become good at, and we also suggest perhaps that OPRR help them get good at through further work in the guidebook based on the kinds of suggestions we make here, in which we identify for the variety of scenarios, whether it's population-based studies that divide things by ethnic group or it's family groups, both of which have an effect on third parties, as appropriate design issues. Why are you using this particular population and not another?

That's what has generated the interest in the Jews is that it is the convenience of the collections from Tay-Sachs that is generating the perception that a lot of genes are associated with Ashkenazi Jewish heritage, not simply that there was something found in those collections. So design issues of why this population, and can you expand the population and still do your research.

Second, advice on how to do community consultations, in which how to identify community leaders that you think might be worth talking to to identify sensitivities that you may not have thought of to see if there's a way around the design. Again, nothing that has to be done. And a bag of tricks that listed things like that.

Then on the "how," there are two possible places where this could come up. One is for IRBs that are already reviewing a protocol because it was supposed to come to them. This can simply be a non-required part of the discussion. We make the following suggestions to you, we do that all the time, to go along with the things that are mandatory.

More radical is the notion that institutions should be encouraged to change their practices and perhaps even embody that in an altered MPA to say that people who are doing exempt research will nonetheless have to have a conversation with their IRB if these issues are present. Very complicated in terms of knowing that you need to self-refer, dealing with the administrator, getting the conversation going. That's more radical, hard to operationalize. But that's the suggestion that was on the table and I promised I would pass it along for Commission discussion.

DR. SHAPIRO: Thank you.

Bernie?

DR. LO: I want to try and tie this section into the discussion Professor Gunsalus had with us yesterday. I guess I would like to suggest that as part of our scut work reduction act for IRBs, we ought to think about what would we really like them to be doing. It seems to me one role that we've not really talked about is they may be the best site for a thoughtful investigator to come and say "I have an issue here that I'm concerned about. Can we talk and let's learn about how best to deal with this?"

To the extent that we're looking for some place for people to think more about these issues, we're not going to settle a lot of things in this report, but if we can highlight certain issues that we think more thought needs to go into and investigators and IRBs and others need to think through, we should highlight these. But also somehow, if that's what we want to do and think in the long run that's going to be useful for IRBs to do, we need to point them to that. But then I think also take away some other things that we otherwise might ask them to do and say we really want you not to be looking at paperwork requirements, but to take the lead at your institution in having substantive,

thoughtful discussion. At least we should present that to some IRBs as something they may want to take on as a mission.

I'm thinking again that what the Mayo Clinic did by spinning off a satellite IRB and having them really develop thoughtful policies and educate their researchers may, in the long run, be something that will do more to protect human subjects than sort of tightening up on some regulations.

DR. SHAPIRO: Bernie, can I ask you a question about that? I think the notion that, and we've talked a lot although not said a lot about it, that the responsibilities that are at play here are not that the investigator has responsibility, the IRB has responsibility, the institution has responsibility, it's a kind of shared responsibility; and the idea that an institution, public or private, might have a place where investigators could go to talk about how do you design experiments, what things you should be sensitive to, sounds to me like a very useful idea.

Ideally, that, in my own sense of it, ought to be separated from the IRB so the IRB maintains a function of saying, yes, this is either satisfactory or not. That's just an alternative. I think the idea is an interesting one, although I'm not sure it belongs in the IRB. We haven't had a chance to discuss. But it's an interesting idea.

DR. GREIDER: It sounds like there is some support for keeping some kind of language relative to this group issue in here. Eric had mentioned that if we have it not be a requirement at all, then it's just not going to occur probably. And to have it be something formal, as minimal as having to write something down, that the IRB reviews I think is a good way to get investigators to actually think about the issues.

DR. SHAPIRO: How is an investigator supposed to know or supposed to imagine that he's onto something, she's onto something, which a large group out there, undefined or not easy to define, is going to be impacted? How is one supposed to reach those decisions? Now there are some obvious cases, we can all generate some, but there are a lot of cases which aren't obvious and the concerns the groups have change over time and the way the groups comprise themselves change over time. How is that supposed to be resolved? How does an investigator know, if we're going to insist, which may not be a bad idea, they write an impact statement like Eric said, how do we know when to do that?

DR. CASSELL: It's the same way they began to discover that there were ethical implications of their work. We all remember in the early days of IRBs, even before the regulations, there were no ethical implications of lots of people's work. I mean, this is just the way it is. But they began gradually, even the oncologists began to realize that they might as well tell the truth. And they did because there was a requirement that they do this. And this is the same thing. We make the requirement and they'll come to know because, after all, there are competitive forces going on in that university and within the

IRB; there are forces acting on them and countervailing forces so that things happen. But you've got to have some requirement, otherwise they won't.

Professor Capron: I haven't noticed particularly if people are competing to be the most ethical.

DR. CASSELL: No, no, but they are competing to get the things through.

Professor Capron: But that suggests—I mean, if you take Alta's point from Karen Rothenberg which suggests a major alteration of the regulations and the requirements imposed by the IRB to take research which is otherwise exempt because it is using publicly available, nonidentifiable samples, for example, doesn't qualify, goes right around the process, right now the investigators send it in, and now the IRB administrator is going to look it over and say, well, it would have been exempt, but we think you may have some implications for groups here, and so at that point you have to file an "impact on others" statement. Is that what—

DR. CASSELL: We'll have to figure out how we make the specification. But certain kinds of work require you to state whether the work you are having might have an adverse impact on ethnic, etc. groups and what might that be? It doesn't have to be very complicated.

Professor Capron: But your work itself may create a group that didn't even exist before.

DR. CASSELL: Yes, it may. But we're not primarily concerned with the little subtleties on the other side of the curve. We're concerned primarily with the center of the curve where people don't pay attention now.

Professor Capron: But I'm not quite sure what this impact statement—I like the idea of people having it in their minds somehow that there are perhaps slightly better or worse ways of going about this. But suppose you are doing a study in which you propose to use stored tissue samples from Tay-Sachs screening fifteen years ago, and the point that it's a study of convenience, you don't have comparable samples from Episcopalians, so what in the end? If you do find that there are risk factors or particular risk factors for a disease in that group, is that wrong to have done it when you know there's going to be an impact? What do you do with that?

DR. CASSELL: Let's go back a step. If Bernie is having us think about it, what are we thinking about? Our work sits here isolated? We were only interested in Tay-Sachs. The fact that a whole population suddenly felt themselves threatened by a disease when, in fact, they may not be so threatened, that's none of our concern. After all, all we did is identify that a certain population has a prevalence of something. What do we care if it got people upset or not?

In other words, the thinking about it is that process. What is the larger impact? And you can take the genes of the prevalence of breast cancer or ovarian cancer as the perfect example of the creation in a group of a bunch of fears that were—exaggerated might be not strong enough.

Professor Capron: Eric, I wasn't kidding when I said that the work itself, even without any ethnic identification, may do that. People like Barbara Lockwood have written eloquently about the way in which research looking at breast cancer has now made women generally more apprehensive about that disease, although compared to other risks in their lives it is not a huge risk. But the fact that there are genetic factors and now the ability to identify two of them, BRCA-1 and 2, has generally elevated concern; and you might say that has caused discrimination, stigma of women generally.

DR. CASSELL: And you don't think that any investigator knew anything about that?

Professor Capron: Well, what do you do once you have that knowledge? I don't understand. If the statement that you're going to file is simply, "If we find a risk factor exists and are able to identify it, all the people who might use this screening test who are potential candidates for the test will realize that they are at greater risk." Period. I'm not trying to be obtuse about this. I'm really trying to think what we expect to come out of this in terms of changes in behavior.

When you talk about investigators not being sensitive thirty years ago to telling people that they had cancer and the reason they wanted to give them experimental radiation was that they had cancer and they had to disclose the diagnosis, I can see both the change in behavior that was expected and a clear ethical mandate for it. With the problems that new knowledge brings, it's harder to understand what change in behavior other than not developing that knowledge one would have.

DR. SHAPIRO: First of all, let me remind you we have ten minutes left for whatever part of this discussion we're going to have today. Alta, Bernie, and Rhetaugh are next. Let's see what they have to say and see how far we get.

Alta.

MS. CHARO: Somehow I feel like around the table among the Commissioners our understanding of the range of situations and the kinds of solutions has not deepened as much as we might like over the last year, which may be why we're struggling to come up with a set of operationalized suggestions what IRBs ought to do. The situations are enormously varied, as this conversation indicates, and there are other situations that arise in IRBs. People want to duplicate old studies and the old studies themselves suffer from these problems. Do you recreate the problems in the name of duplication, or do you now expand your study? We've got studies that are on Caucasians only, for example. So it's

not about stigmatizing the group, it's about not generating generalizable knowledge today.

Perhaps the more appropriate recommendation, which goes to the heart of investigator education, which is really the bigger thing here, is to ask to convene several meetings with people who actually sit on IRBs and people who actually do this research to really talk about the list of situations where this might arise and what some possible solutions might be to ameliorate unnecessary harms to third parties in each of these solutions and create that bag of tricks. And then, with that bag of tricks in hand, figure out where, if at all, it belongs in the IRB process as opposed to a more generalized investigator education. This may sound like a bit of a slide-by, but maybe that goes to the center of the problem is that we don't really know enough to know what we want to accomplish.

DR. SHAPIRO: Bernie.

DR. LO: I agree with Alta that we don't really know what the range of situations and what the range of solutions is. But I think the conversation that Eric and Alex had is exactly the kind of conversation I would like somebody at each research institution to try to stimulate and to have it with, not just in front of, a bunch of investigators who otherwise wouldn't be thinking about it.

And to respond to Alex, I think we should try and be clear in the text that we don't mean don't do the research necessarily for most of the time. But we do, I think, mean things like when you write it up you ought to have a couple of sentences in there saying whether or not there are any implications for Jewish people in your study as opposed to all other people. Sort of explicitly say both in the paper and when you talk to the press, "this doesn't mean that this group is more burdened than other ethnic groups by the risk of the disease.

Also, I think you may then—following with Eric—once as a naive investigator I started thinking about this, I might later on decide, I'd better go talk to some women's advocacy groups and explain my findings to them in lay language, and not just say it's not my problem, I just do the research, but to really do more than that. So I think that the list of solutions, I would like to see us start to develop a list, but I agree with Alta, that list is really not going to come out of this Commission. It is going to come out of investigators, IRB members, and other institutions focusing more attention on it. But maybe we can at least jump-start or catalyze that process, which is not now taking place.

DR. SHAPIRO: Rhetaugh.

DR. DUMAS: I think it is very important that we have something that addresses this issue. I think we need to be careful how we state it for fear it might be seen as a statement that certain kinds of research should be avoided or constrained, and I don't think that's what we intend to do.

I believe that it is possible for investigators to consider these issues and develop greater sensitivity to the possible impact that their research will have on a broader group. I think that there are ways that the results can be reported to minimize a harm, as has been mentioned before, short of withholding information or not reporting honestly, but rather in the way that the data are presented and also the way that the report is written. It can have a certain sensitivity to the impact and make sure that there are statements that would warn people not to go beyond what the data presents.

I'm very much in favor of addressing this issue. I realize there are difficulties in doing so, but I think that's a part of the reason why we need to continue to struggle with this.

DR. SHAPIRO: Larry.

DR. MIKE: Having just woken up, I may repeat what other people said. I guess our discussions in the past around this issue never really involved the IRB review process. It talked mainly about involving group issues in the research design and directed investigators before they even came to the IRB. Maybe we should return back to that focus. The language here tries to leap and make it as part of the IRB process, and I don't recall any discussions along that line when we were discussing this issue.

DR. SHAPIRO: Tom, Carol, and that will be the last two comments.

DR. MURRAY: One of us will be cut off in mid-sentence. I hope it's Carol. I'm just trying to get some closure for myself and for the staff, and for the people who'll be involved in the next draft. What I think I hear is a general consensus among the Commissioners that there needs to be some way of registering—on the consciousness of investigators, at least—the idea that there may be implications for someone other than the subjects of the research. It may be family, it may be some group with which they're identified. We don't know how to do that. In fact, we think that there isn't enough evidence either to fully characterize all the kinds of ways in which this problem arises nor all the possible solutions, and here I'm just synthesizing what a variety of people said. But we can certainly say the first thing—that it is important. We need to think about how to say the second thing. What I'm going to propose is that you dig into your creative potential here and provide some suggestions to the staff and the rest of us about ways in which that can happen.

I think it is perfectly fair for us to say, a kind of "let a thousand flowers bloom," that we think IRBs and investigators need to be more attentive to this and we'd like to see some suggestions from them as to how that might happen. We might suggest some ways to foster that.

DR. SHAPIRO: Carol.

DR. GREIDER: I agree with what you just said. I think that we need to focus on exactly how that gets implemented. Is it at the level of the IRB, or, as Alta has pointed

out, if research is exempt from IRB review, what is a mechanism by which we get investigators to consider this? So I think it has to be a little bit more concrete than letting a thousand flowers bloom.

DR. SHAPIRO: Okay. We have two minutes left. I want to go back to a particular part of the suggestion Alta made that came up a couple of times, and that is the issue of research that is otherwise exempt, and see whether you feel that on this issue, regardless of just exactly what procedure is used, that otherwise exempt research should also sort of fall under this and therefore require review of some kind, call it review for a moment, because of this particular aspect of a research protocol. How do people feel about that? Is that something we want to do? I don't know if it's quite radical, but it is more extreme than the earlier one, that's all. I don't know if it's quite radical.

DR. MURRAY: It narrows the field at least. You won't have pedigrees presumably if it is research that otherwise would have been exempt, or am I wrong about that? Is that correct, Kathi, do you think? But you will have information perhaps about ethnicity. Yes. So that would be the kind of case we'd be talking about.

DR. SHAPIRO: Carol, Alex, and then we're stopping.

DR. GREIDER: So an alternative way to think about this, if we look at the flow chart for determining if something is exempt, one of the questions that you have to answer is will waiving/altering informed consent adversely affect subjects' rights and welfare? We could suggest that at that point subjects' rights be considered—that groups also be considered in them.

Professor Capron: You're looking at the consent chart, not the exemption chart.

DR. GREIDER: Sorry. But anyway, we could fold the group issue into one of the other decisionmaking processes rather than have it be separate. That's the general idea.

MS. CHARO: If I may. The institutions are permitted to exempt from review anything that falls under those Federal regs that say this can be exempt. But they are not obligated to. And many institutions choose to have things that could be exempt nonetheless come before them for one reason or another, and that's probably the place where an institutionalized change could be made, or IRBs could simply institute something, or the deans' offices and provosts' offices, et cetera, institute something much more informal in terms of generalized education that doesn't commit them to any kind of formal interaction.

DR. SHAPIRO: Okay. Alex, and then that's it.

Professor Capron: I think the logic of everything that has been said up until now is that we should endorse IRBs moving in this way. In other words, a good IRB will do

this. Because the whole point of this discussion is that there are interests totally independent of any direct interest on the people whose samples are being used and it doesn't matter if their interests are so attenuated that the research is exempt. So the logic would be, yes, we should either urge regulatory change or urge voluntary steps in that direction.

DR. SHAPIRO: Okay. Thank you very much. I want to repeat what Tom said before. Any of you who have views, and most of you do have thoughtful views, on aspects of this report, if we could get those in writing one way or another, that is a huge help to us rather than wait until our next meeting and then hear from you about what your views are. That's not very helpful because that just prolongs this process. I am anxious to put some pressure on the staff and ourselves to get this report out for some public review. I certainly want to do that in the next month or two. So I really plead with you to, on issues on which you feel strongly and care about, to let us know and let us know in writing one way or another so that we can be as responsive as possible to them.

Let's move on now. Eric, you have some brief reports on some other activities.

UPDATE ON OTHER PROJECTS

DR. MESLIN: Very quickly. I held off giving an update on some of the projects because not all of the Commissioners were here first thing in the morning yesterday. Let me just briefly touch on five things that are under way now both as updates for Commissioners and those who are present.

As I've reported at previous meetings, our protocol project is underway and hopefully nearing completion in the next few weeks.

MS. CHARO: Protocol project?

DR. MESLIN: For the capacity project. The review of protocols and consent forms that have been requested. Trish, Alex, and Jim have been kindly involved in that process. There will be more materials available for Commissioners as this nears completion.

The international project, about which we have also spoken on a couple of occasions, has moved in at least a number of different and helpful directions. We are now about to contract with at least three individuals, I'd prefer not to mention who they are at this point because the contracts have not yet been signed, who will be providing empirical research for us on a number of issues, including the way in which investigators in other countries understand and make use of Federal regulations that the U.S. Government imposes as a condition of receiving funding. There are at least two of those.

That will hopefully be completed, the contracts completed within the next week and we hope to have a timetable that will provide some of that data to Commissioners by

the beginning of 1999 at our January meeting. We hope that by our November meeting you will get to meet these individuals and they can present their research plans and descriptions for you. We're very excited about that because a number of our staff members here, including Elisa Eiseman and Lori Knolls and others, have been working on this project in pieces. I say in pieces, because we have been very mindful of Commissioners' interest in having us complete the projects that are under way, so we have tried to protect staff time on this. That being stated, there are data being gathered and bibliographies being prepared and, I think, very helpful methodological progress being made.

The plan, and I haven't discussed this with Alta or Kathi but I can simply mention it, is that it should not get in the way of any of our other projects. But as you saw on the proposed draft outline yesterday there was mention of international activities. I think that's extremely important for the Commission to think through—whether these projects might be folded into each other or be in some way running parallel.

I am also in the process of trying to recruit an international project director who can lead this project in the way that Kathi Hanna is leading the comprehensive project.

The third item of my five-item update is just to again mention that the International Summit of National Bioethics Commissions in Tokyo, which NBAC is helping to put together, but is not a formal NBAC meeting, has made great strides. There are now about forty delegates from a variety of countries that will be going to that meeting in November, and some of the members of this Commission will also be in attendance.

It is expected that one of the outcomes of the Tokyo meeting may be a statement of cooperation and collaboration between National Bioethics Commissions of the world, or at least of those who are in attendance, of the kind that I think will foster education and work in the future.

The fourth of my five items is something that has been on our shadow agenda, so to speak, and it is the subject of education, one that I know has been of great interest to many Commissioners around the table. I simply wanted to update you that one of our contract staff, Andy Burness, and his group have been very much involved behind the scenes working with Pat Norris and myself and others on staff to develop some of our public communication issues.

Andy has been particularly interested in meeting some of the Commission's needs regarding education. We've had some informal discussions and I hope that at our next meeting in November we can present to you a more fully developed plan for what is under way. But these include such things as updating and making full use of our Web site, discussions about public meetings of one form or another. Some of the Commissioners, I know Bette Kramer, Eric Cassell, and Alta Charo have been

particularly interested in this subject. So I simply wanted to let you know that we are very much interested in this and it is one of Mr. Burness' activities, among others.

The last item, which was mentioned briefly yesterday and I think I'll just let Jim say a quick minute about it, is the meeting relating to the Belmont project. We of course discussed in Portland that the Belmont Revisited project with NBAC's rewriting of the Belmont Report was probably not the best use of our immediate time, but that it was of sufficient interest that some type of adjunct activity could occur.

So I can let Jim maybe just say a quick word.

DR. CHILDRESS: As Harold mentioned yesterday, we've managed to put together independent funding for the conference. Harold and I, with a lot of suggestions from other people, have been working on a conference which will be held April 16-18 in Charlottesville. Some Commissioners are presenting papers and some are serving as respondents, and all Commissioners will be invited to participate in the conference beginning late Friday afternoon or early evening on the 16th and ending around noon on the 18th. You'll be getting more information about that in the next week or so.

DR. SHAPIRO: Okay. Any questions that arise? All right, we'll take a ten-minute break and then reconvene to begin our work on the capacity report. Thank you.

DISCUSSION OF STAFF DRAFT: RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY

DR. SHAPIRO: We hope the rest of our time today of course will be devoted to the capacity report. This is a report which I hope/believe that we ought to be able to issue this year very shortly. I think the report, even though there are some unanswered issues still, is really quite close to its completion. I think it is really our responsibility to finish this report and issue it this year. We should not allow time to go on any longer. I think we're close enough to it and I think we ought to make the decisions we have to make and get on with it and get on to some other project.

I'm going to turn the Chair over to Jim, who will lead us through this project. I think there are a couple of issues at the beginning that we need to have some general discussion on regarding the scope and justifications of the report; Jim will talk to that in a moment, which need to be resolved. And then my proposal is that we go directly to the recommendations, which have been distributed to you. There's a follow-up memo that you all have which corrected some unfortunate slips at the end as we tried to put this thing together. And we'll go from there.

Let me turn the Chair over to Jim.

DR. CHILDRESS: Thanks. Let me start by thanking the number of people who gave public comments. I think we ended up with 87, is that right? Probably some came in after that total. These comments were very, very helpful. And we're grateful to Randy Hull for providing a helpful analysis, and you received that analysis of the comments. As the comments were coming in along the way, it was possible to include points regarding those comments in memos, and some of those points got worked into the draft we currently have.

In addition, I'd like to thank the staff, Eric Meslin and others, including Jack Schwartz, who has joined to help out with the discussion, in particular relating to the use of various kinds of advanced directives, but other parts as well, and Cathy Hollen, who has been serving as an editor on this.

As Harold mentioned, if we look back over the discussion we've had here in meetings and the e-mail exchanges that have occurred, as well as the various conversations, two preliminary concerns perhaps need to be addressed before we look specifically at recommendations, and they certainly will have an impact on the recommendations. Those two concerns have to do with the scope of this report—and we had some exceedingly helpful comments on the e-mail, I found myself changing my mind after reading one and moving to the next one—and then the justification for the report. So if the Commissioners agree, let's start there and then move to the recommendations.

I would note that you've received memos that address the issue particularly of scope, and I'll just connect the justification issue with that. Some of the changes that are incorporated into the current draft try to focus a bit more why we have chosen the direction we have chosen here and what implications that might have. But I would note that this was a matter of particular concern to the respondents and that 52 of the 87 respondents addressed the question of scope; that's 20 more than addressed any other topic. So it is something that we do need to make sure that we're clear about and that we can offer an appropriate defense for.

Let me just make a couple other comments and then let's see where we want to go with it. We initially started out as I recall by looking at a decision on cognitively-impaired or decision-impaired research subjects. But throughout, the focus has been on a particular population. I think in the e-mail exchanges that occurred from, say, mid-August on, there may be more agreement than might at first glance appear. Let me just throw that out and let me offer two different ways in which one might approach this matter.

One is what I might call a build-up strategy. You might start in the report from those with mental disorders, and I'll just use that as a shorthand expression rather than going through "that may affect decisionmaking capacity," et cetera, that are the subject of research, and this is where the report currently moves, I think. But then to indicate, perhaps even more than we do here, although we do have some suggestions along these

lines, that these principles and guidelines apply to others who are decision impaired or cognitively impaired as well.

So that's a kind of a build-up. You start from focus on this particular population and then you move from the particular to the more general, and you can say more or less about that. There might be a variety of reasons, some of which we include in the report, historical reasons, social reasons, concerns about vulnerability in the context of research and so forth, for concentrating on this particular population. That would be the build-up strategy.

And we could have a build-down strategy, which was suggested in some e-mail messages, that would start from the principles and guidelines and say these are the things that apply across the board, but there may be particular concerns with the population we address in this report, and we will look at this population for illustrative purposes.

Now those would be two different ways, and I think I sensed both of those in the e-mail exchanges. What I want to emphasize is that they end up, I think, pretty much at the same place but with a difference in emphasis. That is to say, one can give a variety of historical and other reasons for concentrating on this population, but we still have the question of the general applicability. It seems to me one of the big issues is how we're going to balance those two matters.

The second point, and there are others as well, about focus would have to do with mental disorders versus some other formulations, or whether to include brain disorders and the like. But let's start with the first one and then see where we want to go.

DR. SHAPIRO: Okay. Let's focus on this before we get to the recommendations.

Bernie?

DR. LO: First, I want to thank Jim and Eric and the staff for really doing an awful lot since our last meeting to sort of collate—

DR. CHILDRESS: And Harold who agreed to everything all the time.

DR. LO: And Harold, going through this responses, trying to make sense of them, sort of taking a lead in suggesting language and responses. And I agree with Jim. As I read through most of that thick stack, I was really struck with how many of our respondents had very strong concerns about the focus, the title of our report. I think it really goes beyond that because many of our recommendations are phrased as "for persons with mental disorders that may affect decisionmaking." We single them out in the recommendations.

I was very concerned at the feeling among many respondents that by singling people out in this way we're actually doing them a disservice. That the very group we

were trying to help might end up being stigmatized as a result of a possible reading of the report that says that if you have a label of mental disorder attached to you, somehow your decisionmaking capacity will be suspect in the research context and all these “protections” we put on you.

But actually, it stigmatizes you in the sense of really singling you out on the basis of a categorization, not on first cut on an individualized assessment, particularly in the context of we know there are many, many other conditions that are not usually thought of as mental disorders that impair decisionmaking capacity in a research context. And as I thought about that, I was really persuaded that our emphasis on mental disorders was not necessarily the best approach and that we really are talking about persons with decisionmaking incapacity in a research context. Mental disorders is just one pathway by which you may arrive at that.

So I would just like to say I really want to rethink our focus on the mental disorders and am concerned about the responses we got with regard to singling out people and perhaps stigmatizing them.

DR. SHAPIRO: Alta?

MS. CHARO: When I began to work through this I also became persuaded from the comments that it would make more sense to work from generalizable principles that apply to all people with impaired decisionmaking, although I fully understood why it might make sense to urge IRBs as they begin to implement these recommendations on a voluntary basis to perhaps focus their efforts on those people within that population who have impaired decisionmaking capacity who seem to be most likely to be subject to inappropriate enrollment and use as human subjects. That might well be the population of people not with all mental illnesses, but with just certain mental illnesses that are particularly problematic in terms of interaction with others.

One of the reasons that I felt this to be true is that as an ethics body, it is valuable I think to recognize the logical extension of principles. And the principles here are really based upon the respect for people who cannot consent consistently over time for themselves, and under what circumstances can they be drafted into medical research.

The second is something that comes from an analogy to the world of epidemiology and public health law. I was very impressed once by an author named Wendy Parmett who talked about democratic versus undemocratic illnesses. That when one divides up a population into special subgroups and begins to make rules for them—for the poor, for the disabled, for immigrants, for people who are ethnic and racial minorities—there is a tendency by the majority to not see their own interests implicated and to be more draconian in one fashion or another. But when rules are drafted in a way that’s going to apply to everybody, one tends to take a more balanced view because you might be the recipient or the enforcer of the rules.

Now in the world of impaired decisionmaking, we have classic, very difficult debates over other scenarios. The granting of a waiver from the consent requirement for people who are in need of emergency medical care is a wonderful example. In that particular area there was the argument that without being able to do unconsented research on these people, important research would not take place. And this was fought out over years, and the decision in the end was to permit it only when there was a situation in which the experimental protocol was possibly of direct benefit and, at worst, was neutral because there was not standard therapy that was working. In other words, they were working through the same kinds of principles.

What I fear, if we were to focus on those with mental illness and then try to build up from there, is that we might find ourselves developing a set of rules that as they build up turn out to be somewhat inconsistent with the rules that are also being developed for other populations of people with impaired decisionmaking. That we might be safer testing every one of the rules that we're proposing here against a whole variety of populations and asking are we willing to live with it for all populations, even if we're only going to start by applying it to one population, and in that way get a nice balanced view at the end.

DR. SHAPIRO: Laurie?

MS. FLYNN: I'm very heartened to hear this discussion. This has been an issue even within those of us who deal around advocacy for individuals with mental disorders on a daily basis and, in fact, has been one of the most fervently debated points amongst members of my organization. Indeed, I think we have come to feel that the points that Alta and Bernie made are persuasive. That we do not want to, by virtue of a diagnostic label, make some assumptions and lay some particular and special categories of protection that really may not in the end be helpful.

So I think we'd do best to broaden the scope as we focus the report, recognize that decisional impairments affect a larger group than just those with specific mental disorders and yet pay attention, as indeed I think we have throughout our deliberations, pay attention to the particular vulnerabilities that we have learned are particularly attended to certain of these disorders. So I would favor us moving in the build-down strategy, as you described it, rather than the build-up strategy.

DR. SHAPIRO: Larry?

DR. MIKE: I clearly disagree, and you know I disagree. This is kind of late to be talking about expanding beyond the people who have impaired decisionmaking because of mental illness, because that has been the whole focus of our almost two-year discussion. Why this comes up now at a critical time or toward the end is beyond my comprehension.

DR. SHAPIRO: Other comments?

Diane?

DR. SCOTT-JONES: As I reread our justification for this report and I listen to the comments about how it is important not to stigmatize any group of people, I agree with that. But I suppose when it comes down to getting this report done, I would have to agree with Larry that we made a decision a long time ago and I don't see how we can change this easily in the time that's remaining to us. We would need to change the whole justification for the report.

DR. SHAPIRO: Rhetaugh?

DR. DUMAS: I have always seen this project as having very broad implications for people who impaired decisionmaking capacity, and I have seen the choice of the case in point as people who have mental illness because this is a population that has been seen as being particularly vulnerable. So I don't see these two concerns as being necessarily oppositional.

I believe that there is value in targeting the mentally ill because of the cases that we reviewed earlier because of the concerns that people have had. But I do think that we can make statements early on, if we haven't done it already, that this is a special case. What we're really talking about is people who have decisionmaking incapacities. And I don't see anything in the report that is not applicable across a wide range of diagnoses.

DR. SHAPIRO: Eric?

DR. CASSELL: Everybody knows how I feel about it. But I would like to ask people who think we ought to focus on other conditions, would they tell me what other things that afflict the human condition; affect decisional capacity; wax and wane over long periods of time; are accompanied by defects of judgment secondary to misperceptions of the world, which also wax and wane over time; and which are susceptible to treatment to remove those two defects. If they can tell me anything else that doesn't come under what we've discussed here that fits that category, I'd like to hear what it is.

DR. SHAPIRO: I'm not going to answer that question, while I have some views on all this. But let me go to the Commissioners first.

Professor Capron: I would support Rhetaugh's basic approach here. And it seems to me also that it isn't inconsistent. And what I would ask, in response to Alta and Bernie, is that as we look at the recommendations we ask ourselves is there anything said here that we would only say of a person who had a diagnosed mental disorder or disease or would we say it also of a person who because of some other problem was unable to make a particular decision? And if we get to something of that sort, then ask ourselves why are we separating out this group.

But the basic notion that we have studied this area, come to conclusions, and then could say these same considerations ought to be taken into account by IRBs as they review protocols that involve subjects who lack decisionmaking capacity for other reasons, I think that is a better approach rather than trying to rewrite the whole report now.

It is not this report that is going to stigmatize people with mental disorders. We are dealing with this issue precisely because that stigma exists, the system doesn't deal well, our country doesn't deal terribly well with people in this condition and they have been vulnerable to a level of problems in research which I don't think has been matched by many other categories of research. And I think if it were matched by other categories, we'd be looking at those categories. If cancer patients, it turned out, were suffering as many harms to which they weren't consenting and were sort of locked out of view for a good deal of the research, I think we would address cancer patients, yet we wouldn't say we're stigmatizing cancer patients by that special concern.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I would ask that we look at the other populations that have been singled out in the regulations, and they're footnoted on page 9: pregnant women, prisoners, children. I think the case of children in particular is instructive because that category includes adolescents, many of whom have decisionmaking capacity approaching that of adults and we still consider them a special category in general needing special considerations. That's not to say that there is never a child who cannot make a good decision about research participation, but that, on balance, it is helpful to have children as a special category.

I think we can say the same to justify our treatment of persons with mental disorders here. It is not to stigmatize them, but to say that, in general, we need special considerations and we might recognize that these regulations might not be needed for specific persons in that category, the same way specific persons whom we categorize as children might not need the special regulations.

DR. SHAPIRO: Bernie?

DR. LO: Let me just try and respond quickly to some of the points others made. I think there are other conditions that wax and wane that affect decisionmaking capacity.

DR. CASSELL: Give me one.

DR. LO: Delirium in acutely hospitalized patients.

DR. CASSELL: Over years? It's transient.

DR. LO: It's transient, but if you do research on them and they are delirious at the time, you're in exactly the same situation as if you had relapsed from...

DR. CASSELL: It's unarguable. Something in these regs will protect that. They'll be protected also.

DR. LO: But my concern is that when you read our recommendation, it says people with mental disorders, not people with other disorders that also have a very high likelihood of impairing decisionmaking capacity.

I think in response to Diane, I want to say children are different. The presumption with children is that you're not competent and adolescents are an exception to the rule for children, so we're going to treat them like adults. That's different from the way we treat most people. Adults, the starting presumption is that you're competent. Now by virtue of having certain conditions, mental disorders is just one of a number of conditions, we may have good reason to question that.

But once you single someone out and say we're questioning your decisionmaking capacity because you have this, this, or that, we are singling them out. And it could be for very good reasons, but it could also be singling them out in ways that are maybe not so desirable. And I think of all the things that could cause decisionmaking impairment, in our recommendation to single mental disorders out from all the others singles them out in a way which I don't think is fair. We're not treating similarly situated persons similarly.

DR. SHAPIRO: Rhetaugh? Excuse me, Alta first, then Rhetaugh.

MS. CHARO: Let her go.

DR. SHAPIRO: Okay. Rhetaugh?

DR. DUMAS: I think that we need to be careful about our wording so that what you just said, Bernie, is not the interpretation. Because certainly it is not my view that we are saying that people who are mentally ill are ipso facto incapacitated to make decisions. What we're saying is that those people who are mentally ill who have incapacities need extra protection. And we're also saying that efforts should be made to ensure that this assessment is appropriate and expertly done.

So it could be anybody who is ill who may have problems in making decisions and judgment. I think we need to make clear in our report that we are not saying that all people who are mentally ill have difficulty in making decisions. That is not our intent. And if that is the interpretation, then we need to do whatever is necessary to avoid that interpretation.

DR. SHAPIRO: Alta?

MS. CHARO: I believe, Larry, that the reason why this came up at this particular late moment is because the public comments were taken seriously and they raised this issue and suddenly everybody began grappling with it. And I think that is exactly what

ought to happen as a result of the public comment period. So I'm not disturbed by the late arrival of this issue again.

For me, a central problem in medical research is about its underlying justification. And I've used the phrase "medical draft" many times, which some people might think of as being extreme, but I do think of the enrollment of people who cannot volunteer for themselves as a form of a draft for the public good and, occasionally, for their own personal benefit. And that's extremely problematic and needs to be approached very cautiously.

So I find that to not address the situation with regard to the general population of people with decisional impairments, even if transient, because I never understood this report only to apply to people whose capacity fluctuates over multiple years, I understood it simply to apply to people who had decisional impairments, although in this case with mental illness. I find that it is important for us to emphasize that unconsented research that poses no prospect of direct benefit to the subject and is more than minimal risk should not be imposed on people. People should not be exposed to this without their consent. Prior consent, fine. Elaborate use of surrogates that have been appointed to make these decisions for them, fine, because those are all ways in which people essentially have said I'm volunteering in one fashion or another. But to simply ignore the fundamental principle that people should not be exposed to more than minimal risk for no benefit to themselves without their personal involvement in that I think is simply a hard line that I would encourage we drop. And I don't want to see us draw it only around the population of people whose impairments arise from mental illness. I think it's really more basic as a human rights question.

On the other hand, to conclude because I know I'm going on too long, I'm not suggesting, however, that we rewrite the entire report. I am suggesting specifically that the recommendations be written without reference to mental illness, that the report emphasize that as IRBs begin to implement this that they might quite appropriately focus, as we did, on the population of people with mental illness, for two reasons. One, the frequency of impaired decisionmaking is going to be higher in this population than in the general population of patients as a whole because of the nature of the disorders. It won't be universal, but the frequency will be higher so you'll be seeing it more often. And second, because there's a special history here that adds to the prospect that that impaired capacity will be taken advantage of in some fashion, deliberately or not.

So we don't have to change the entire report. We may need to change the first couple of pages and the actual wording of the recommendations, and in every other respect the report can stay the same, in which mental illness is the running example of a broader problem.

DR. SHAPIRO: Trish, Larry, Steve, Eric, Jim, and then I have a lot to say about this. Let's see, who is first? Trish.

MS. BACKLAR: Actually, Alta, thank you because now I don't need to say a great deal. What I was really hearing there was an argument between speed and content. I think that Alta has kind of put those both together and taken us off the hook. I do think that her suggestions are very good.

DR. SHAPIRO: Steve.

MR. HOLTZMAN: I was just going to observe that I'm hearing two very, very different strands of thought here. The one that Alta just articulated has to do with whether or not we should be making recommendations—the class of people to whom the recommendations should apply, and I'll come back to that in a second. That seems to me very different from the question if in choosing a class we thereby stigmatize and therefore we ought not choose a class. I think we should run those two arguments together.

If we're going to follow Alta's procedure, I think the way you have to do it is what Alex recommended. In your way, I think the way we've articulated, is we took a case study, if you will, for good reasons, we've reached conclusions, and now you want to apply those conclusions beyond the case study.

The only way to do that is to look at each one of your conclusions and ask would there be any reason why I wouldn't apply this more broadly. And after you've asked that, you're going to say have I really thought through all of those other cases so as to be able now to generalize, or does it take another year and a half to feel the same confidence with respect to that broader application that we needed the year and a half to get to this smaller group.

DR. SHAPIRO: Eric.

DR. CASSELL: Well, I think that's a very good comment. I don't think anything in these recommendations does not apply to people who have lost decisionmaking capacity for other reasons. Nothing.

I personally think it stigmatizes people not to allow them to be who they are. And that in the whole current business of people who are decisionally challenged and vertically challenged and optically challenged, an attempt not to be what you are is a kind of negative stigmatization. And I'm not the only person to say that. Lots of people do and for good reason. In fact, there aren't other disorders that produce this particular problem, the particular population that has been punished by not being protected, singled out for many reasons but all of them leading to nonprotection. To focus on the decisional capacity is to focus away from the special protection that a population needs because of the trouble they have.

You don't want to call it mental disorders, call it trouble, call it anything, but it is a special population and it's a painful population for themselves and for others. We set

out to do this, they were excluded from previous protections, and that's what we should do.

On the other hand, I absolutely agree we should never permit research done on people who have no decisional capacity without protections. And these will take care of that. But I don't think we should hide from a special population because we're afraid that the name is bad.

DR. SHAPIRO: Jim.

DR. CHILDRESS: This has been a very helpful discussion, and I know it's not over yet, there's more to come. But it does seem to me that we have in the suggestions that have been offered a plausible way to go and that certainly Alex's suggestion is I think a very good one, that after we feel comfortable we have all the issues out on the table that we need to keep in mind about scope and justification, then the exercise of going through the recommendations and really seeing what we have with this question in mind as to whether what we have here applies merely to the population we've focused on or whether it does have a great generalizability. So I think Alex's suggestion is an excellent one.

DR. SHAPIRO: Larry.

DR. MIKE: Well, you've already heard my opinion. But I just want to comment on Alta saying that the reason that this discussion is going on is because of the public comments. It depends on how one reacts responsibly to the public comments. It doesn't mean that you go and change your whole assumptions and all the work that we've done. You try to allay the kinds of fears that have arisen that we're singling out.

I would violently disagree that just because we're looking at this issue because it arose in the area of mental illness and fluctuating capacity or varying capacity that we, therefore, stigmatize them. I don't accept that premise. I think that there are other ways of dealing with that public criticism than just wholesale transformation of our report. People are saying it applies to a whole lot of areas. But we've never had that discussion. We've always focused basically on the people with mental illness. We have not had that wide discussion over this period. And to leap to a report that all of a sudden changes that is something I can't agree on.

DR. SHAPIRO: Diane.

DR. SCOTT-JONES: I agree with what Larry just said about how we should respond to public criticism. It isn't to completely change our goal in this report, but to be mindful of what might happen when people read and interpret what we've written. I think it means that we need to reread our sections in the beginning, where we justify why we've chosen this population and I think we can make a strong and convincing case. I think Alta's suggestions for focusing on frequency of impairment and the history of the way this population has fared are excellent ways to emphasize that we had a reason.

But we're not saying that every person who fits in this category is the same. No matter how you break down categories you always will be subject to the criticism that the way you draw the boundaries isn't quite right. That's just the nature of categorizing individual human beings. You will have some variability and you will have some fuzziness at the boundaries of that category and people who don't fit that category.

So I think our strategy should be just to reread and make sure that we've crafted the language as carefully as possible not to permit misinterpretations of what we're about.

DR. SHAPIRO: I strongly agree with what Diane and Larry have said. I think we have to go back to the beginning here before we lose track and put ourselves at sea totally. It's very interesting to me that of the long years we've been working on this and the public comment we received, that issue never arose before except at this table, where it arose right at the beginning when we asked ourselves this exact question. Because immediately at this table the issue came up: What about other people whose decisionmaking power is impaired? And we discussed that and made a decision about it. And we have spent a year and a half or so thinking as carefully as we can about this issue.

It is not at all clear to me if you go through our recommendations that we can possibly, in the time we have reasonably available, understand whether it applies to everybody who ever has a decisionmaking impairment. I completely agree with Alta's commitment, as we all do, that people in that situation should not without some protections be drafted, as you say. I completely agree with that. But we looked at this issue and we took a particular branch. It may or may not have been the right one. I think, myself, it is a perfectly defensible one.

Of course, whenever you talk about a special population you are guaranteed to get this response. That's just the nature of public rhetoric today. And if you don't talk about it, you'll get the other response. And you can be sure that if we had broadened this and took the opposite view, we would now be getting comments, perfectly respectable, thoughtful, and from people of good will and knowledge, that, in fact, we had missed the boat because within that group of occasionally decisionally impaired, transiently decisionally impaired, permanently decisionally impaired people there is a special group whom we haven't taken the bother to notice.

Now I think it would be quite inappropriate for us to try now to expand this to include another worthy subject—this is a worthy subject, other people who are decisionally impaired—to expand this to include them. That's not what we focused on. That's not what we have asked. After all, we have had public comment not only at the end, but we had public comment every time we have met, and we have had people meeting before us at virtually every meeting on this issue, none of which raised that because they understood what we were dealing with. And I interpret the public process

we're involved in, it would be not quite within our contract to expand at this stage. There's a whole series of people out there who may have wished to address this if we were doing the broader thing.

So I think, however, that there are important ways, indeed, we have a responsibility to respond to the very thoughtful public comment we got at the end, and I think we have to find ways to include that in the language of our report, make it clear. This report, if you read it from the beginning, goes even at the current time to great lengths to try to make the point that having a mental illness is not per se ipso facto meaning you're decisionally impaired, particularly with respect to your decision to participate in a research protocol. That has been on our minds right from the beginning in every draft that we have produced here, both the good ones and the ones that weren't so good.

And so I just think that short of remobilizing over a long period of time that we really don't have the option of the broader population. We could make that decision that we want to remobilize over a much longer period of time. I think that's not a good strategy. We have too much on our agenda that we have to address.

We're about to do something useful and helpful and I think we should go ahead and do it and in as spectative way as possible. And if we think that there is another extremely important population which we have to deal with, we can add that to our agenda and, using this material, proceed to make additional recommendations. None of that should prevent us from making sure the language here is appropriate and is as responsive as possible. None of that should prevent us if we think we have a particular recommendation that need not mention or at least doesn't benefit from singling out a population (like people with mental disorders), then we could always not phrase it that way. But the idea that we could on the fly remobilize ourselves to deal with a much broader population, which has a whole series of issues we've never even discussed at this table in some cases seems to me too risky and not responsive, mainly not responsive.

And so that I think our choices are—I don't know, Jim, I haven't thought of it build-up/build-down analogy before. I think we've just got to work as imaginatively as possible with the build-up strategy, if I understood what you were saying, and use the public comments, many of which were very thoughtful—indeed, I learned a lot from reading them—in ways to improve what we're saying and to make sure what we're doing. I don't think any fair-minded person can read this report and accuse us of stigmatizing people. I just reject that accusation. It has to come for some other reason or not having read what we said carefully. But we need to try our best to even use language which avoids that as much as possible because it wasn't anyone's intent here.

So while we can go back and say way back then we should have made a different decision, well that's possible. I certainly wouldn't want to defend that more than that. But we made a very sensible decision even though there were other sensible decisions we

could have made. And so I think our challenge is to make sure the language we use is as responsive as possible to these concerns, which are real and important concerns. I don't want to belittle those concerns in any way. Those are real and important concerns. But in terms of our agenda, you all know what projects we have in front of us are we just have to get on with it.

We're on the verge of doing something very useful and about which there's a long literature that says, somebody should have done something about this twenty years ago and thirty years ago. And here we are about to do something about it and stand some chance here of getting distracted and pulling back from that. I think that would not be wise. Bernie?

DR. LO: Let me go back to the point that Steve raised, which I think is a very good one. Let's put aside for a minute the title, the framing, that sort of thing. Let's go back to the recommendations, which are really the core of what we're doing. And taking account of what Harold just said, how do you all feel about looking at the recommendations and trying to see if we can make the recommendations without specific reference wherever possible to mental disorders?

Responding to Larry's concern and Diane's concern, and Harold's concern, we just haven't thought about how this would play out in other scenarios or situations where people may be likely to remain, in fact not have decisionmaking capacity, do we feel confident phrasing recommendations which are broadly worded enough to apply to other types of situations that we really, frankly, haven't thought about except that criticism?

But I just am concerned that it is accurate to phrase our recommendations in terms of people with mental illness because that's what we thought about. But I think the question is do we single out our recommendations to apply only to them, or to all people belonging to a category that has a high potential for not having decisionmaking capacity, or to all people who, in fact, do not have decisionmaking capacity. We're struggling with a problem of are these three groups ethically similar in relevant ways. And if so, should we treat them the same, or should we treat them differently, or should we just say we never thought about it, so we'll just state it in terms of the narrowest framing that applies to what we did?

DR. SHAPIRO: If I could just interrupt, Jim. I think we should go to the recommendations very shortly and just see as we go through, as a result of this conversation, understanding, and see if we can improve the language in ways that we feel comfortable with that's within our capacity and knowledge to deal with. And so I'd like, Jim, if it's all right with you, in just a few moments to go directly to the recommendations, because we can talk a long time about all these issues because it is an important but inexhaustible source of discussion.

So I would like to go directly to the recommendations at least very shortly. Now I have three people on my list and I want ask them if it's all right if we do that, and it's Trish, Alta, and Steve. But if not, we can wait and you can say a few other things.

MS. BACKLAR: I can say what I have to say very quickly. One is, I feel like you yesterday, whoever speaks last, I am persuaded. But actually, I am very persuaded by your argument. And I am also actually persuaded by Alex, who I thought was the person that said that we should look at these recommendations as though we're looking at the issue of capacity to consent. And I think that that is the issue. That's why we're having so much trouble, because what this report's about is people's capacity to be medically drafted or to make their own decisions about going into a research protocol.

And I think if we examine—I agree, if we examine the recommendations, we may find that we've resolved in ways things that we can easily change what goes before and use what goes before as something of a paradigm, not as just this particular group. I think it would be quite easy to do that.

DR. SHAPIRO: Alta?

MS. CHARO: Far be it from me to not be persuaded by an argument about pragmatics. But my concern had not been about stigmatizing. And so I would like to urge as Plan B, if people don't object, I'd like to urge that we have an extremely strong, simple to understand statement right up front that says "Risky research with no benefit on people who can't consent is morally suspect." Period. We are focusing on the mentally ill. Much of what we say is going to be applicable to others. I know it's there. It is not clear. You have to wade through 200 pages to find that concept in there. I would like that to be emphasized, not the stigma issue.

DR. SHAPIRO: I'll turn to Jim. I have no problem with that.

DR. CASSELL: I think it actually says that in the first sentence of the second paragraph quite clearly.

DR. CHILDRESS: I think the revision does go more in that direction. But, again, I think we can easily go back and—

DR. SHAPIRO: We can meet that challenge.

Steve.

MR. HOLTZMAN: Just very quickly. I agree with that. I took Harold to be saying what I said to Bernie: that the methodology would be to examine the recommendations but that you couldn't without going back for a long time be confident in terms of the general applicability of those. So that we could certainly go through this exercise now, but there is no way I, for one, would feel confident in the generalizability without then asking the questions who else, and by putting it in that and engaging that. And I took that to be Harold's argument.

DR. SHAPIRO: That's correct.

DR. DUMAS: There are some that are written there generally. Many of the recommendations do not have the words "mentally ill" in them.

DR. SHAPIRO: We'll get to all of them momentarily.

Jim, how about taking us to the recommendations.

DR. CHILDRESS: All right. If—

DR. SHAPIRO: Excuse me. I apologize again for interrupting. You may also want to refer the Commission members' attention to the memo that you addressed.

DR. CHILDRESS: Right. I thought we would go to the draft text and then I'll refer you back to the memo for particular discussion.

So the first recommendation is about IRB membership. That appears on 139, our recommendation number one.

DR. SHAPIRO: Larry?

DR. MIKE: I'm going to have to leave about 11:30 or 12:00. So if we don't get to the areas in which I'd like to say some comments, I hope you will indulge me in interrupting.

DR. SHAPIRO: Okay.

DR. CHILDRESS: How much time would you need?

DR. MIKE: Let me just raise the issue. If you look at recommendations 4, 9, and 10, and I believe it's the revised 12 and 13. I read that to understand that—even those without the actual personal capacity to consent could be enrolled in minimal-risk research. In more-than-minimal research, there's a distinction between with benefit and without benefit. I think I raised this issue in some of our e-mails. I don't understand the distinction why. I see that at least for the area of "more than minimal risk with no direct benefit," there's been a change. It effectively says people who will never have the capacity to consent can never participate in research with minimal risk and no benefit. I had some problems with the dichotomy that we had there, where before that was left in and then people with some fluctuating capacity could participate only if they had an advanced thing. That still remains in the "not greater than minimal risk/direct benefit" area. It puzzles me about the logic behind that.

DR. CHILDRESS: Right. And Alta has raised a similar point with relation to that specific recommendation. So we will make sure that that's dealt with.

So we'll just go in order then.

DR. SHAPIRO: But you've noted that down, Jim?

DR. CHILDRESS: I've noted that, and Alta has also raised it this morning privately with Trish and me.

Okay. The first recommendation has to do with IRB membership. We did get public comment on that and the staff recommendation was that we basically not make any change in this. Is there any discussion of recommendation number one on page 139?

DR. MIKE: I guess the discussion also says that—we're only talking about IRBs that regularly deal with these kinds of research topics. But I think the text adequately addresses that concern because it just depends on a particular situation, and IRBs that don't regularly deal with these will not have those members. The numbers are a toss-up. You can never agree on those specific numbers.

DR. CHILDRESS: And I should just note here that at times we've actually had the rest of the paragraph following the boldfaced Recommendation 1; we've sometimes had that as actually part of the recommendation. Here it is presented as text. But it has been at some times part of the formal recommendation.

DR. SHAPIRO: Bernie? Jim, why don't you recognize people so we aren't confused.

DR. LO: I have two concerns about this recommendation. I think they both can be fixed. One is that I think we're under-inclusive. I'm actually very concerned about IRBs that don't regularly consider these sorts of proposals but get one handed to them. I think I would like to have something there to say that in that situation we strongly encourage an IRB to go out and get special expertise and discuss with—

DR. CHILDRESS: We do say that. It's in the text but we've sometimes had that whole first paragraph as a bold recommendation.

Professor Capron: What is this language that is indented as a paragraph and it stops being bold?

DR. CHILDRESS: I would prefer we go back to the way we've had it in the past, which is this is all recommendation number one. That whole paragraph.

DR. MESLIN: Up to line two on page 140.

DR. CHILDRESS: Right. And that I think would take care of Bernie's concern here.

DR. LO: Yes. I'm just concerned that it be part of the bold recommendations. That's one.

The second concern has to do with the generalizability question we were discussing earlier. Could we put in a paragraph in the text saying IRBs that regularly deal with proposals with other classes of people that are likely to have impaired decisionmaking capacity consider getting input about—because you're singling out...

DR. CASSELL: Who are they? They are a clinician, Bernie.

DR. LO: Eric, in my hospital and your hospital there are a lot of drug studies for pharmacokinetics on hospitalized patients, many of whom are not competent to consent, the consent form is signed and they have no idea what they're getting into.

DR. CASSELL: Bernie, that's covered, clearly covered under existing regulations. They are not permitted to be included in research because they can't give consent. Now if in your hospital they are doing that, what are we going to do?

DR. CHILDRESS: Alta?

MS. CHARO: Eric, I beg to differ. That's exactly the problem. They are being included routinely.

DR. CASSELL: Even though the regulations prohibit it?

MS. CHARO: Other people are consenting on their behalf—routinely—but without any of the special limitations, protections, audits, and monitors that are being proposed here.

DR. CASSELL: I'm saved by my phone. Hello?

Professor Capron: This is all on the transcript, Eric.

DR. CHILDRESS: The question is would it be possible though to accommodate Bernie's concern by either a footnote or parenthetical comment or separate paragraph?

DR. LO: Let me just say something. Steve and I had a side conversation. The category here, I think it would be good idea to have an IRB have someone who is not just a lay member but someone who has insight into what it means to be in the hospital, a former patient, a relative of a patient, a relative of an ICU patient is another category. What I'm concerned about here is people saying shouldn't we also have similar consideration. And I would say, yes. And we don't have to state it because we haven't thought it through, as Harold has so nicely argued, state it as a recommendation, but say IRBs ought to at least consider it so that we keep the issue out there.

DR. CHILDRESS: Diane?

DR. SCOTT-JONES: It seems to me that that's already covered in the language that we have. On page 140, it states "It is for these reasons that the Common Rule directs those IRBs that frequently review research involving a vulnerable subject group to consider having as reviewers persons knowledgeable about and experienced with working with the relevant subject group." It is already in there to cover other groups.

DR. LO: But we had a small conversation before about membership on the IRB with voting rights and sort of being an ongoing for the process is different than being a reviewer. I just think that we're not losing anything by putting that in and it signals that

we're aware that there are other groups that you can identify by group category that share many, if not all, of the characteristics of people with mental disorders.

DR. CHILDRESS: Mr. Chair, if it would be permissible. One possibility here would be actually to get Bernie to draft such a paragraph or a few sentences, not necessarily right now, so that we could then decide whether it was something that we could comfortably include.

DR. LO: Sure.

MR. HOLTZMAN: Bernie, I, for one, and I think most people would agree with the spirit of what you want to accomplish. The question is can we possibly do it here and is here the right place to do it? In general, if an IRB sees a lot of AIDS cases, it would be useful to have representation. If they hardly ever see them and they have one, they should get someone from the outside. The question is in the context of this report are we going to end up footnoting everything we say by saying one should consider the generalizability of this for all similar, where similar is so wide open? That's the concern I would have. And at the end of the day, we may have vitiated the impact of this for the problem we're trying to address.

DR. CHILDRESS: Eric just mentioned, and I was on the same wavelength, that this might be exactly the sort of thing that the White Paper could well address.

Harold?

DR. SHAPIRO: One alternative, Bernie, to this situation, which doesn't address this particular one but as we go through this, as Steve says, if we try to accumulate one more paragraph after another here, it may be difficult. One alternative is to go to the area we have here somewhere called "Guidance to IRBs" or something like that and try to lay out much more carefully there how they, advise them that they should really look at this set of recommendations, think about other populations and consider.... I don't have the words, I'm sorry I can't get the words out right now. But that might be a way in which they might actually notice it more because it would be highlighted in one place and thought through carefully. Maybe that would be a good idea and would save us having to tailor-make it.

DR. LO: I like that suggestion better than my suggestion.

DR. CHILDRESS: Steve, a follow-up here, and then I have Rhetaugh, then Larry.

MR. HOLTZMAN: And also maybe we want to explicate right at the end, right out in bold, that in considering this, there are great lessons that have been learned that in fact are probably generalizable. And maybe we could specify there where we think the direction of thought should go.

DR. SHAPIRO: Give us a chance to do it in one place. And we can also do it more carefully. Give it more attention.

DR. LO: That's a good suggestion.

DR. CHILDRESS: Okay. Rhetaugh?

DR. DUMAS: I'll be brief. I like the suggestion that just was made. I'm not in favor of changing the wording of recommendation one because I think it would dilute it or even confuse it. I think there are two suggestions that make a lot of sense to me, and that is to make a statement at the beginning in here, and also to treat the general issue in the White Paper. I thought that would be a good idea.

DR. CHILDRESS: Laurie?

MS. FLYNN: I wanted to make sure that we had some agreement. As I think you were indicating, Jim, that we would like to have the whole of that first paragraph become the recommendation. I wanted to support that and I didn't know if we'd come to some closure on that.

DR. CHILDRESS: Actually, let me emphasize, the whole has been the recommendation until this draft and then somehow only the first sentence became bold.

Anything else on this recommendation?

DR. SCOTT-JONES: And are we agreeing that we should move or strengthen the paragraph that says "additional guidance for IRBs" on page 157 that refers to the spirit and substance of these protections? Were we saying that we might consider moving that?

DR. CHILDRESS: Yes. We will do that. We will draft something.

Okay. Anything else on 1? Recommendation 2. Following public comment, the staff recommendation was for a more careful statement of the justification for this particular recommendation. The draft you have before you—the text, I think, does go some distance toward providing stronger justification. It may not be there yet, but it will focus on the principle of fairness and on respect for persons in terms of informed consent as particular reasons.

Eric?

DR. CASSELL: Just a simple thing. Could we take the word "targeting" out? I don't think we want to target a population. I think we could just say "involving" persons.

DR. SHAPIRO: That was an issue we went over. I don't know about targeting or not. But what we were concerned about, as I recall, Jim, was we did not want to prevent people with mental disorders from participating if they are able in some research

project just like any other person would. What we wanted to do was prevent those people being taken advantage of as a group, or that's how I understood. That's where targeting came from. I'm quite willing to think of better words.

DR. CHILDRESS: I think I proposed it but it was just a way to get at exactly the point that Harold has made.

DR. SCOTT-JONES: Singling out, focusing on?

DR. DUMAS: A lot of people understand the word target, and so I would disagree with Eric. I think that in the general concepts in which we're talking, the word target is appropriate. They understand what you mean when you're talking about focusing on a particular group.

DR. CHILDRESS: At any rate, we will provide suggestions and we'll see what will work here.

Larry?

DR. MIKE: I think part of the reason for the objections that we have received was that mistaken notion that if they were heart disease, period, we're saying they can't participate. So I think on page 142, the lines 20 and down should be more prominent. It is sort of buried down there. I think we should make it clear that we're not saying that they should not participate in research in these non-mental health areas if they are related to the condition that they have.

DR. CHILDRESS: Okay. We'll work on strengthening that part then.

Any other comments on Recommendation 2? Okay. If there's no objection, we'll turn to Recommendation 3. Recommendation 3 on assessing potential subjects' capacity is the one that received the second-most public comment; 32 of the 87 addressed this. Here I'd refer you to the memorandum of 9-15, page 1. This is the one from Harold, Eric, and myself, dated September 15, Supplemental Materials. Here there is an effort—if everyone locates that, it was at everyone's table yesterday—it's an effort to deal with this in part by going back to what had been a part of our discussion earlier but then got lost in part because of the location of this. This was really limited to research involving greater than minimal risk. That was the trigger for this kind of systematic assessment of competence of subjects, not that competence is not assessed in other settings, but this is a requirement for the systematic examination.

So that is the major change that is recommended on page 1. And, again, it goes back to our written and oral tradition here, but that doesn't mean that that resolves anything.

DR. MIKE: Jim, I think the placement is what confuses people, too. It should be later on.

DR. CHILDRESS: I think that's right and I actually have recommended that we consider doing that. One of the things in looking back over the materials leading up to this is we had, in addition to the flow chart appendix, we also had another appendix that just summarized the recommendations. And in that particular one we had it clearly targeted earlier in a different location: what would be appropriate for greater than minimal risk research. That may be a way to handle this to avoid the confusion. Because it was confusion that came up in our discussions with some other groups when they said, but look, this is going to be terrible in the research area, and we responded, but look, we're only talking about greater than minimal risk research for some of these things at this point.

Eric?

DR. CASSELL: I understand that, and I understand the objections investigators have that this would be time consuming and expensive. There is an implication, however, when the method is specifically stated otherwise that this is one of those places that you can enroll people in research without being able to make consent. If we say you only have to assess when it's greater than minimal risk, the implication is you don't have to be that careful when it isn't there. I think we ought to say that ability to consent—to understand—is necessary for all research, however....

DR. CHILDRESS: Okay. Bernie?

DR. LO: I want to continue that line. I think you always need to assess the capacity of your potential subject to consent. I think what we're talking about here is a formal assessment using some kind of validated instrument, and you've thought about why that instrument rather than some other—another strand. I agree with the notion that that level of more formal assessment only kicks in on the greater than minimal risk.

And then there's a third strand here, which is the independent assessment by someone other than the researcher on the project. I'd like to seek that out a bit because that's a really big change we're recommending. I'd like to talk and think a little more about what the implications of that. I know where it comes from. I think it's a well-meaning and an appropriate attempt to address the serious problems of conflicts of interest when you want to enroll your subjects; and subconsciously or otherwise, kind of deem them competent even using a formal capacity assessment.

DR. CHILDRESS: Harold?

DR. SHAPIRO: I'm just asking a question for clarification here. I agree with what I believe Eric and others have said here, that this ought not to be phrased as a way of saying here is a place, a big wide loophole, so to speak, where you can go without consent. That wasn't what was intended here but it's not clear, I think, from the way it's written. And so I do think that we need to rewrite this to reflect what Bernie and Eric both have said. We still have to worry about this, it's just you don't have to have this

formalized instrument dealt with unless it's greater than minimal risk. So I think some rewording here is necessary. And I think placing it somewhere else, Jim, as you suggested, is also a good idea.

DR. CHILDRESS: Okay. I assume there's general agreement about doing something along those lines just to make sure that we don't get off the hook too easily.

I have Trish, Alex, and then I think Bernie, and then Laurie.

DR. BACKLAR: What is interesting to me about this particular recommendation, I'm thinking of psychosocial research and I think of any protocol that goes through NIMH is going to be scrutinized on the human subject section, and anybody that I know of who is doing psychosocial research is going to be very careful that their potential subjects have capacity for consent, and there's a whole lot of different pathways that one goes through this. I think this alerts us again to the terrific problem of that kind of research that goes on in this country which doesn't go through Federal funding in some way. And I just want to alert you and your paper to looking at this because this is a very good example.

We've read many different reports. I don't want to refer to it because I can't think of the precise reference, but different reports where we have found that people are doing research with subjects whose capacity for decisionmaking may be somewhat impaired who are not going through those funding streams where we watch them. So that's all, just to alert to that.

DR. CHILDRESS: Alex.

Professor Capron: In light of Trish's comment and Eric's, I want to be clear about why we are limiting this to greater than minimal risk. If one has a subject with potential lack of capacity, and the thought is, well, we do an assessment, Bernie says, we don't have to use an instrument that meets as high a standard as this paragraph would require, we don't have to use an outside expert, we can do it ourselves as researchers, and the thought is either that we will say a person has capacity and get consent from them when they don't really have the capacity, or, conversely, we will say that they don't have capacity when they do and we'll get consent from someone else, which we're permitted to do because it is less than minimal risk. Am I correct in understanding that? That in a certain ironic way the risk of exploitation, although probably not the risk of physical harm, is at least as pronounced in so-called minimal risk research as it is here.

If that is the case, I don't understand the reason for the revision that is proposed in your memo which limits it to the more-than-minimal-risk setting.

DR. CHILDRESS: First of all, I would emphasize that it's a revision only in the textual sense. We look back at the way we've treated it all along, I think it's not a revision, it's actually capturing what we had suggested. But that doesn't get at your

other important point. I guess in a number of these areas we are having to make certain assumptions about reliability, trustworthiness, et cetera of investigators.

I think the concern here, as I recall our discussion, would be the fact that if you're going to have an appropriate method, validated, et cetera, and the independent expert, we're talking about a very strong, heavy, and costly procedure many would say for certain kinds of minimal risk research of the sort that Trish mentioned. And the question would be whether that's the sort of thing we want to require here.

I happen to agree with you about the risk of exploitation. I think we want to be very attentive to that. But, in part, it's a question of what we hope to accomplish, what sorts of things we want to protect at different points. That's the way I would interpret what we're doing.

Professor Capron: Do we have any evidence that people conducting one category of research or another, minimal- or more-than-minimal-risk research, are more likely either intentionally or unintentionally to make errors in assessing capacity?

DR. CHILDRESS: I don't think we have that. I think it is the risk of harm.

Professor Capron: So it's the risk of harm rather than the risk of exploitation; that is to say, being used without your consent. Yet a few moments ago Alta said that the report should begin with a clear statement that people are not to be used in research without their consent, were not to be drafted, and we all shook our heads and said, yes, that's a basic thing that we all agree with.

I actually, thinking as a member of an IRB, would think that the risk is certainly there that an IRB facing what is described and what they think already can be called less than minimal risk will be precisely more likely not to think hard about "is the method of assessment a good one, is there enough independence, or are we going to get, as I say, either people can't consent being called people who can, or people who can being called people who can't so that their surrogates can be asked and give permission for them?"

MS. BACKLAR: May I say something?

DR. CHILDRESS: Before I respond to that, let's go over here.

MS. BACKLAR: I think that we have to sort of think about the kinds of studies that I might be alluding to, where there are interviews or questionnaires. And if somebody can't consent, they're not going to be stabilized enough, they're not going to be able to go through the interview process, they're not going to be able to answer the questionnaires. And often these studies are involved in looking at outcomes over a period of time. I'm thinking about my psychiatric advanced directive studies, where I couldn't bring people in that didn't have capacity to consent in the beginning because I wouldn't be able to start off with that.

Professor Capron: So for that group it's a self-correcting process.

MS. BACKLAR: Absolutely. And I think that's what many people were referring to, they are very concerned. There are a lot of epidemiological studies; these kinds of studies that go on across the country and they are very important in terms of the benefits that may occur, not necessarily in the study itself, in following this group of people.

DR. CHILDRESS: Let's see, I have Diane.

DR. SCOTT-JONES: I have a concern that's a little bit different from what has just been discussed, and that is that I think the recommendation should reflect a little bit the language on page 71, that discusses the difficulty in evaluating decisional capacity and also points out the capacity performance distinction that one is always only assessing performance at a given point in time. So I would suggest that the recommendation lead investigators to employ an appropriate method carefully specified and justified to reflect the language on page 71, that points out that capacity assessment is not at all easy or straightforward.

DR. CHILDRESS: Laurie?

MS. FLYNN: I'm not sure I understood exactly what Trish was trying to say. But I am very happy with the way this recommendation has developed and feel that the addition is an appropriate one, or the inclusion of making this focus on research that is of greater than minimal risk. I think to try to impose this kind of requirement in all research, basically of any category, not only creates an enormous additional burden in research that we've not seen any demonstration—or I've not seen any convincing evidence—that it is necessary or is ameliorating a problem.

But I think, again, it tends to reinforce the notion that it is this category of people regardless of anything other than their illness label that we have to have these extraordinary additional kinds of supports for regardless of the risk involved in the research. So I was comfortable with the way we brought it forward here.

DR. CHILDRESS: Okay. Eric wants to get on, and I have Alta, then Bernie.

DR. MESLIN: I was just going to indicate this may be another place where the Guidance to IRB section, which may become a very useful and expanded section in this report, could profitably recommend the distinction Bernie was trying to make between formal capacity assessment and those areas where IRBs may wish on their own accord, we do mention that in the document, to take this up if they see fit.

DR. CHILDRESS: It may be useful to have it here as further explanation of the recommendation for the kinds of concerns that Alex and Bernie have mentioned.

Professor Capron: If we had non-bolded language as a paragraph following this that said that, what Trish just said, that in many of the circumstances of minimal risk or less the concern is self-correcting because you can't do a questionnaire with a person who lacks decisionmaking capacity, they won't be able to answer the questions. I'm not

clear that that's the case, but I'll accept your view that that must be the case. But alert the IRB that there may still be some "less than minimal" where they may need to have some additional assurance from the investigator as to the quality of the assessment process.

DR. CHILDRESS: Trish wants to respond.

MS. BACKLAR: I just want to amplify that. It's capacity for the task at hand and that's very much how we usually assess capacity anyway. So if you can't do it, you can't do it.

DR. CHILDRESS: Alta?

MS. CHARO: Two things. First, do I understand correctly that any expression of dissent on the part of the subject will be honored in both minimal and greater than minimal risk?

DR. CHILDRESS: Yes. And we'll come to that.

MS. CHARO: Okay. In that case, one of the harms that Alex had suggested, which is that inappropriate finding of incapacity yielding a loss of autonomy on the part of the subject and a third party being able to make decisions and enroll the subject is also ameliorated because the subject still can dissent and that will be honored. So that's a second correction you might want the note to clarify.

Part and parcel of all of this was a slight concern on my part that the wording of the recommendation now is slightly at odds with the text that follows on the topic of presumption of capacity versus presumption of incapacity, because recommendation number three as written in the memo says that it shouldn't approve these research protocols unless the investigators employ appropriate methods. It strikes me that somehow that raises the inference; it's not clear, but when I read it it raised the inference that every time a greater-than-minimal-risk protocol, or perhaps amended here any protocol greater than minimal risk, or striking the IRB as unusual comes before them that the immediate thing they're going to do is require formal capacity assessments for every subject. And I believe that your intent is probably reflected more in your discussion, which is that the IRB is simply supposed to be looking at each of these and asking is there any reason here why we need a more formal assessment than we usually have? I thought you might want to think about rewording the recommendation to say the IRB should scrutinize the protocols, as opposed to automatically requiring...

DR. LO: I wanted to shift the discussion a little bit away from the using of an appropriate method for assessing capacity to administer by an expert independent of the research team. And I think clearly that this recommendation comes out of some of the individual cases we've heard; for example, discontinuation of medicines for schizophrenia, where in that situation the stakes are very high if you have a person entering a protocol as a result of a flawed assessment capacity, it's a terrible tragedy. But

in our deliberations, in which we said, we're going to only have two categories of risk, minimal risk and everything that's not minimal risk. We kind of applied it, we're applying this now to everything that is greater than minimal risk, including the very, very potentially risky things to the just a little bit above minimum risk. And I understand the reason for having two categories and that's a good place to draw the line. But, I'm not sure that having, I'm not sure that requiring an independent assessment by someone on the research team is as valuable when it is only a little bit more than minimal risk, where it's clearly desirable and needed in the much greater than minimal risk category. Let me give you two examples. One is a research that involves not just questionnaires. Trish was talking about questionnaires that deal with sensitive subjects like drug abuse, which is often a crossover with mental illness. Many IRBs deem that greater than minimal risk because of legal implications and such, and I think rightly so regard it as more than minimal risk. But it seems to me it's a little more than minimal risk—not a whole lot more—and there is again that self-correcting as an investigator who is told “you've got to use a standard validated instrument, not just your clinical assessment.” That's a good protection. Having it, and it's self-correcting. No investor is going to want to enroll people who aren't going to be able to give meaningful answers to the questionnaire, which overlaps to some extent with giving consent to the research. So, I think we may be overly broad there. I think that the other example I keep thinking about is research that's more than minimal risk in a sense that it involves an MRI scan or a CAT scan in someone who may have mental illness, and the argument is that that is more than minimal risk for someone who may be more likely to get anxious or upset by the procedure. Again to remind ourselves that there are several other protections in that situation that have to deal with if they dissent at the time of enrollment, you're not going to enroll them anyway and if they dissent at the time the procedure's being done, you're going to have stop the procedure at the time. So again, the likelihood in that situation of someone being sort of being pushed into a study when they don't have the capacity to say no is not as broad as would justify this kind of recommendation for that class of research. I think that the final part of it is, I think that research is valuable research and needs to be done. If we don't do that kind of research you're not going to get therapeutic benefits down the line, and I think we have to ask ourselves. We have a good intervention for a certain class of research that presents a very high likelihood of serious problems with entering a patient who doesn't have the capacity, but we're now extending it to all research that is greater than minimal risk, and I think we've taken a good idea and extended it too far.

DR. CASSELL: Could I address that directly? I'm confused because I heard earlier in the argument how the investigators in your institution enroll people in research who have no ability to consent and they do that regularly. And now I understand that you don't want to make it harder for them because this will make it difficult. I can't have the two. Either your investigators in your institution have to have their nose to the stone or they don't.

DR. LO: Well, Eric, yes. It depends on the clinical situation, okay? An investigator who has a study that involves MRI scans or patients with schizophrenia, by virtue of our other recommendations is not going to be able to enroll that subject if the patient says I don't want to do it, even if the investigator misses the fact. Also, if they balk at the time of the study, they're not going to enroll.

DR. CASSELL: How about the one that wants to please the investigator, really wants to make him happy because they want to make sure that they still get fed or that there's a blanket on their bed so they want to do everything they can do to make, they happen to be incompetent at the time, but they're doing that. How about that person, never mind the one that dissents. How about the one that consents when they shouldn't consent? Remember it works both ways.

DR. LO: Okay, and the question I'm asking is, is requiring an independent assessment by someone not on the team for protocols that present only a little more than minimal risk worth all the effort that it's going to involve?

DR. CASSELL: Then you have to go and make another risk category because otherwise you're going to have that same problem we had with this before. You get stuck in that risk thing.

DR. CHILDRESS: Okay, I have Carol, Steve and Alta.

DR. GREIDER: I just have one quick point. When Alta said a minute ago just to reiterate that dissent from participation in research is true across the board, whether it's minimal risk or greater than minimal risk. That brought up the fact that Recommendations 3 and 4 are now focusing on greater than minimal risk, and a dissent comes as Recommendation 5. Maybe the order should be switched so that it's clear the dissent comes before we start talking about greater than minimal risk.

DR. CHILDRESS: I think that's an important point because, and I've been struggling with this myself, because the notification or termination of capacity to enroll in research can apply to a variety of settings, whether you've done the formal, systematic, heavy-duty assessment or not. As you have determined it. And so it's, 4, as I would understand it, is broader than 3 in terms of the population reply to. And 5. So relocation of what is currently 3 would be, I think, important for clarifying that. Let's see, Steve?

MR. HOLTZMAN: Two comments. I've gotten a little bit confused as to what we're recommending, so at least analytically, I'm trying to break it down into the following parts. I mean I think the sense is here that we want the bar to be higher in certain cases. So the first question is what constitutes the bar? I think it has two parts, a formal assessment and an outside expert. Okay, I'm simplifying. The second is when is that higher bar in play or potentially in play? I'll come to that in a second, and I think it is when it's greater than minimal risk. All right? And then the third is it mandatorily in play

or is it discretionary to the IRB? Like, for example, if you make it mandatory then you're going to have Bernie's concern about minimal risk and that, on the other hand, the way to ameliorate that is by making it, I think this is what Alta might have been saying, by making it not mandatory but rather the IRB discretion and then take it into account. So I think it would be useful to sort of break down what it is that we are recommending in that. The only other comment I have, and then we'll come back to Recommendation 4, is that we just say "lack of capacity" and we don't modify it as a result of mental illness. And I think that we have to just generally come back to that.

DR. CHILDRESS: Well, as it currently reads, and this is under the part of the regulation, this would be mandatory, okay? And on the other issues we have to decide as to where we want to go. We could put this somewhere else, but at least to this point it has been treated as a regulatory requirement. Alta?

MS. CHARO: I'd like to return to Bernie's comments. Bernie, I want to understand better something about your comments before; you can think about responding. I'd like to understand whether what you are now questioning is the need for a particular methodology for assessing capacity; that is, a formal assessment with an independent auditor, or whether it's you are beginning to question the need to ensure genuine capacity to consent with regard to what you would call this class of research that is just a little bit more risky than minimal risk. I want to know if the objections to the methodology because it's cumbersome, or to the real need to consent, to get real consent.

DR. LO: No, it's to the former. I think, I agree with you. You need to give informed consent or else you have to make sure that any other path that enters the patient is an appropriate one. And I would separate out the using of a formal assessment tool versus having someone other than an investigator carry out that assessment. Because I think the implications of having someone else do it are very profound. We need to make sure that that's what we want to do.

MS. CHARO: All right. There are people here who have better memories for what actually happened on the transcript than I, but I suspect that the reason why this got written up the way it did was because of a feeling that without a simple rule to apply, that too much discretion on the part of IRBs and too much deference to colleagues might reduce the number of times that there is an insistence on this cumbersome mechanism to a diminishing few. All right? And that in most cases even with risky research, IRBs and investigators would say that we know that there's going to be a truly ethical assessment of capacity and we don't need all this rigamarole. And I guess then I would want to suggest that we focus the discussion on whether we need to constrain, whether we want to constrain IRB discretion through this kind of mandatory procedure or whether we simply want to write it with a strong suggestion to them. Keeping in mind that everything we do in here is advisory so they'll only implement what they feel like implementing anyway, and if it ever gets to a regulatory stage, that the regulation writers

will also be responding to the pressure to ratchet back a little from what might be, argued to be, an excessive degree of solicitous attention on our part.

DR. CHILDRESS: And again, Steve's identified the guiding lines here, but we are going to have to make some choices. But before I turn to Harold, though, it's important to keep in mind that we're trying to reach as much consensus as we can. But I'm sure there'll be places where several individuals will file a separate statement, personal statement, in which they say well, I'd like to amplify this or we should have gone further there and that sort of thing. Keep that in mind. I think that's something that the document will inevitably have given the kinds of divisions that exist on some of these important matters. Harold.

DR. SHAPIRO: I just want to clarify in my own mind, Bernie, your point. I think I understand it. The, see phrase, "administered by an expert who is independent of the research team." Now that phrase has two qualifiers. One, you have to be an expert. Two, you have to be independent of the research team, and it's the independent of the research team that you think is especially cumbersome, or both. I'm asking a question.

DR. LO: I'm more concerned with "independent of the research team." To go back to the conversation Eric and I were having, I really think we've responded to some very awful stories we've heard about, cases. And they were characterized by a lot of, they had a lot of qualities. They were institutionalized patients who were much more dependent and vulnerable, Eric. There were situations where the investigator was also the responsible physician in some sense, the personal physician of the patient, which really ups the ante for a conflict of interest, and the nature of the protocol was such that these were very sick patients who were going to have a very high chance of relapsing from their condition, either by natural history or by the intervention. And all those together create a scenario where I would say, yes, that IRB should have said let's make really sure these people have the capacity to consent as well as a whole lot of other things downstream, which we'll get to later in the report. But to take those protections, which are totally appropriate in that situation, and then say the IRB should also do it across the whole range, that's what I'm questioning. The expert thing gives a lot of wiggle room because I'm not sure who an expert is. Is it a professor who specializes or is it a research associate trained, the way I would train a research associate to do anything else in a competent fashion. I don't know.

DR. CASSELL: Well, I think that the expert problem is a real problem, but by someone independent of the research using a validated instrument, or using an approved, an instrument of which the IRB approves, but it ought to be somebody independent of the research. But it doesn't have to be an expert. It doesn't have to be the guy who designed the instrument to come down and test everybody and find out if they passed his instrument or not. So anybody else could do that too. But the independent of the research is what makes it, is what protects the patient. Now the other issue to bring up is unarguable. The problem is, what is arguable is the minute you do that you now have

more than two levels of risk, and we're back to the argument about well, what is that risk level and if you say serious risk, you know we get into all those questions. So what you're bringing up is very important and we once again, I wonder if we'll ever have a discussion here that doesn't come back to that minimal risk thing and risk that doesn't get us out of that. But that's where we are, right? So you have to say to yourself, either put the qualification in a way that really works or you just have to accept this.

DR. CHILDRESS: Let Bernie respond and I have Trish and Steve.

DR. LO: Or have some other means of having some nuanced approaches rather than having an absolute, "it has to be this way." So either you can have an extra category for risk or you can have some, a little bit of discretion when they apply it. But the more you get simplicity, you also worsen the problems of this application of a general principle.

DR. CHILDRESS: And the issue, and Steve raised it nicely earlier in terms of kinds of decision points we have on this, again the reason this receives so much attention from public comment is that it did seem to be unduly burdensome. And by limiting it to greater than minimal risk we open it up a bit, but the other kinds of questions that are being raised, we are going to have to come to some decision on.

MR. HOLTZMAN: I think Eric's hit at the point; it's instead of casting it, do you believe there should be multiple categories, it's really if, with the best intentions to protect human subjects, we keep tightening down each element and then you take a step back and you say there is some research which is not going to take place which we really think is important. Then the question is where are you going to open it up and it, if you feel that way, I certainly don't want on each recommendation say we should change this recommendation. But I also believe that if you loosened every one of them, that wouldn't be right either. So where do you pinch it?

Professor Capron: We talked about a version of that yesterday, Steve, with valuable human materials which are, which a researcher would love to use but if we require certain things and they can't contact the person, they lose it. We're talking about something different here, it seems to me. We're talking about the extra costs with more-than-minimal-risk research of having a qualified professional, which is the term that I would substitute for an expert, a qualified professional, independent of the team, do the assessment. And what are we concerned about? We're concerned about a person being recruited in who doesn't have the capacity, and is said to have the capacity, or recruited in under somebody else's say-so when they do have the capacity. Now if it's the former that's the main concern, it seems to me that that is something which, as the example Eric gave of the person who doesn't dissent, who goes along, is something we should avoid. Having someone give consent to something which they're not capable giving consent to. And if there is some research which is made more difficult because you can't use that person, it is different than saying, we have a wasted resource where, what's the real harm

of using it, it's just some cells here and so forth. This is a person who will be involved in more-than-minimal-risk research on their "own" consent whereas a person independent of the team looking at it and applying about qualified instrument would so, no this person doesn't really have the capacity to make that judgment. That is a cardinal example of some person who shouldn't be in the research. Shouldn't be used on that basis. And so it is not a matter of preventing something good that should be happening, it's a matter of preventing something bad that shouldn't be happening. And I have no problem there toward the recommendation. My suggestion, however, would be that we actually have recommendations 3a and 3b, and 3a apply to everyone, not just, and that is that the investigator be asked always to use an appropriate method to assess the subject. In other words, rather than my curbstone sense that this person is fine. It doesn't seem to me that it is inappropriate for IRBs to be told that they should always have as part of protocol review, where the subject is potentially incapable of making decisions, a statement that their capacity to make the decision will be evaluated according to the following validated protocol, which takes five minutes to run through. But it's a checklist of questions you ask them and responses you're looking for and if you think they don't make it they don't make it. Not by an independent person, if it's less than minimal risk, because the chance of getting someone in is apparently regarded as acceptable because they're, it's only minimal risk. I would prefer that we apply it across the board. I can see that that does not have majority support but I would at least say that as to the less than minimal risk, there's no reason not to say you ought to have a protocol for doing it rather than just your curbstone sense. I can't understand what our objection to that is. In what sense is that an inappropriate burden to place on someone?

DR. CHILDRESS: Could I respond and then Harold, I think I passed him earlier when it was his turn and promised to come back. I guess one of the questions would be what sort of presumption we work with and what triggers the assessment. By going to the greater than minimal risk, we're saying that here you're going to have to do the formal assessment because it's greater than minimal risk. In other kinds of settings, what triggers what kind of assessment seems to me is the question, and whether you're working with the presumption that all the people with mental disorders that may affect decisionmaking capacity are people who have to be examined carefully. Or whether other kinds of usual informal source of procedures serve as triggers.

Professor Capron: Well, my sense is that there, would be no harm in that other discussion we have of sort of IRBs ought to be thinking about this to say to IRBs, when you're dealing with patients in the ICU or patients who are otherwise heavily burdened by illness and so forth, a question of are they, under the circumstances, able to make their own, to make judgments about going into research ought to be evaluated because their thinking may be clouded, to say nothing of their independence of their doctors and so forth and so on. So I have no problem saying this is again the case study and then we're sort of thinking this may have generalizations but we're not yet ready to write a requirement for all those other categories because we haven't looked at all of them. But

IRBs could well think about this. So the notion that the research community as a general matter has not given enough attention to the assessment of people's real capacity to make judgments about going into research seems to me to be a perfectly valid thing to suggest that we ought to be more concerned about. The fact that it hasn't been done is not conclusive to me that it shouldn't be done, to put the point briefly.

MS. CHARO: It strikes me during the course of this discussion that on a related but tangential topic, maybe the part of the struggle here has to do with the way in which the recommendations are being organized. They've been organized around the question of the audience, to whom are they directed, IRBs, government, States. It may be that if they were organized in a fashion that was more chronological, the process of working with people as this study population, that some of these problems may get a little easier to describe. So it's something to think about. Because doing it that way, one might go, people should be allowed to participate in research when they're able to consent. Next. Is there a reason to believe somebody's consent is not valid because they lack capacity? And that, then we turn naturally into a recommendation in which IRBs are directed to look at every protocol for any sign that in this case, the subject population is likely to contain people who may not clearly be able to, may not have the capacity and where it may not be obvious, so that more careful assessment has to be made. Or, at the risk of stigmatization but in light of the kind of consequences of how we are doing this report to say, IRBs should whenever dealing with research protocols that involve people with mental illnesses that are implicated in decisionmaking processes. There are mental illnesses, like bulimia, that have nothing to do with your decision making with regard to ruling on an MRI study, but some forms of mental illness are associated with disorders of thinking. So where you as IRB see a disorder that's associated, mental disorder associated with problems in thinking, here's where we want you to stop and assess whether special evaluations need to be made and, as the risk goes above minimum, that scrutiny should happen more and more frequently. You should be erring on the side of using these methodologies but because we're doing it chronologically, I think it gets a little bit easier to see it in some kind of context, and that's also where you can emphasize that the availability of dissent is an automatic withdrawal. It took place with this. It's a corrector on a failure to do this properly, and that that should be taken into an account but not used as an excuse to avoid any capacity assessment. I'm just wondering if this might help us kind of work through it in a more integrated fashion.

DR. CHILDRESS: I think that's right, though, I think that we would still have to raise the question of whether we want to bullet some of these things and say yes, but you're going to be required to do this. This is not some guidance. It seems to me that question that still comes into play.

MS. CHARO: You know, I'm beginning to feel like we would be better off if we were to direct attention strongly without creating mandatory impositions of requirements, because I'm always aware of how difficult it is to write generalizable rules

that cover situations perfectly. I'm highly aware of the problem of IRBs doing work that seems to be inappropriate or investigators jumping hoops they think of being as inappropriate creating a disrespect for the entire system. I'm not persuaded that IRBs and investigators are untrustworthy enough that they can't actually implement this, but it would have to be very strongly worded with, and this is where my lawyer training comes, presumptions that. The presumption is that if it is more than minimal risk, you're going to wind up using an instrument unless you're pretty sure that you really don't, in this particular case. The presumption is that if you've got particular kinds of disorders you're going to wind up using an independent expert. And that gives people the wiggle room they need to exercise some discretion and not feel bound by rigid rules that make them do silly things.

DR. CHILDRESS: I think we're going to need to wrap this up. But there are still several points we have not, I think, reached any consensus on and I thought Steve identified those well and now Alta's come back to the one about whether we want to make it mandatory or not. Each of those things will make a big difference so we will need to see if we can reach some general agreement, again knowing that there will be some dissent from this. Larry.

DR. MIIKE: Coming from Hawaii, I like to fish or cut bait. I think we should reach some decision but let me just mention two things. One about the issue about mandatory versus of leaving it up to the IRB to decide on an individual basis when the risk is of serious enough of level to require a more formalized procedure. I think that's the choice that we should really decide on. The second part is to address Alex's concern about the adequacy and why not say that just in any kind of research involving people with impaired decisionmaking. That we should have a more direct approach to ensure that their consent is possible. I think one way to do that is when we, if we follow through with our most formalized assessment with people with greater than minimal risk either in a mandatory way or a discretionary way, I think what we should point out is that investigators, the research committee and the IRBs should take a look as that process goes forward about whether it raises questions about the more informal way in which they've assessed capacity to make decisions, and that that would be a way of saying hey, if it's really deficient that we got it, we have to take a second look at even though less than minimal risk. So it's sort of like built into the process, a self-correcting measure or an assessment of the occurring assumptions about the adequacy in the minimal risk area. But I think our current focus on greater than minimal risk is that we want to impose a burden commensurate with the risk. That's what we're doing, and I think we would argue forever, Alex, about whether we want to impose that on a lower size. So as long as they build a process into, I think it can be self-corrected.

MR. HOLTZMAN: I very much agree with Alta's way of thinking, where we need some word in here about appropriate; that when dealing with putting aside stigmatization. We're dealing with the population where antennas should up in any

research. That's the first step, because there's the possibility of not genuine consent. And then we're saying that when the risk goes up, we want to raise the bar higher. But what I would ask Alta to think about is the desire not to make it mandatory, because what you're recognizing is the ineluctable rule of judgment here. All right? But what we want to do is provide clear guidance as to where the judgment is being exercised. In other words, whether or not to use a formal capacity to assess an instrument in an outside expert. If you are saying that should be left to judgment, it should be because what you're focused on there is in this judgment that's not necessary. It shouldn't be because, well, it's only more than minimal risk. So what I'm afraid of is since all these pieces interlock, that we don't want to be opening up valves here and there where people make it the gemisch again. I fundamentally disagree with Alex's characterization of what I was saying. I'm not trying to squeak things through; I want us to be clear, so we give people clear guidance, and we're trying to make something happen, or not make something happen. Let's just be clear about it in where it is, and where it is disagreements, we can articulate them. I don't want, if I believe that there are certain kinds of research that may get blocked by these recommendations, I don't want to squeak it through by making believe I have consent when I don't. That's not what I'm saying Alex. Okay?

DR. SHAPIRO: Am I correct then, I'm just trying to catalog in my sense, the concerns that are swirling around on this particular item. One is the issue, what happens when it is less, when it is minimal-risk research? What happens there? And there was some initial discussion here around the table that no matter what kind of research it is, somebody has to be responsible for some kind of assessment. You can't go ahead and knowingly use people. We sort of left that there and Alex's suggestion, as I understood it correctly, under Recommendation 3a, which specifically addresses that issue; that is, if you just have less, if you just have minimal risk research you are required some formalized assessment, characterized as simple but it was formal, it wasn't just the curbside judgments. And then, so that's an issue, first, that we need to clarify. Do we want to, is it necessary and helpful to highlight what happens in minimal risk research regarding assessment of capacity? Then there's the greater-than-minimal-risk research of what this supposedly addresses directly and there I think there are two issues that perhaps divide us. One is whether it ought to be by someone who is independent of the research team, and the other is the issue Alta raised, is that whether this is normally required or always required? Those two, I'm just trying to understand if those are the issues in front of us, and if they are, Jim, maybe we should just go at them one at a time. Let's start with the minimal risk research one and say what we want, if anything, at this point on this issue.

DR. CHILDRESS: I think that's very helpful. Steve, does that fit pretty well with what you remarked the issues?

MR. HOLTZMAN: I think so. The one comment I make, Harold, you almost have a "step zero" there, though. Is there a fundamental presumption that the antennae

should be up with respect to the issue of whether we have genuine consent with this population? We've written language here where we want to make we're not stigmatizing and we say you know, you're capable unless not. But I think the issue about whether more than curbside judgment in any and all cases—depending we could go much higher—only arises if you start with the presumption that the antenna should be up on the issue of whether or not you have genuine consent, you have the capability. If you don't start with that presumption, all right? That's where our focus should be and then we raise the bar as a function of risk. It's not risk that triggers that question.

DR. CHILDRESS: Okay, I think Harold's proposal is a very good one and I think that's one way to resolve it. If Trish also wants to address aspects of that so we could just go through the parts and see where we stand?

MS. BACKLAR: In terms of minimal risk, obviously one still must assess capacity to enter into a protocol because one would do that with any group of people. And so that I think, I don't disagree with that. I agree there must be some, not assessment, but certainly an informed consent process in which the person agrees or disagrees and when you're going through that, you're making some kind of assessment at that particular point anyway.

DR. CHILDRESS: Right. Bernie. Oh sorry, Alta?

MS. CHARO: I was going to try to answer Harold's question.

DR. CHILDRESS: Okay, go ahead, go ahead. Bernie, I'm sorry, I've got to come back to you.

MS. CHARO: It seems to me that someone could answer your series of questions by taking it from the point of view of an IRB, and it would almost be like a checklist. Checklist item number 1, is there a population that's going to be studied that raises our antennae about their capacity to consent? If the answer to that is yes, then has the investigator explained how he or she plans to make sure that the subjects genuinely can consent? Number 3, is the research more than minimal risk? If yes, has one challenged the investigator or explained why one wouldn't need to have an independent expert doing the capacity assessment, and in that fashion one could work through connection of these two factors. But this does use the presumption as opposed to the mandatory approach.

DR. SHAPIRO: One word changes that whole set of recommendations. I mean, you follow through the minimal risk and your checklist, and only at the end—your last recommendation—had the presumption rather than the mandatory.

MS. CHARO: That's correct. That's true.

DR. LO: Let me first say, I like Alta's suggestion. I think giving people visual flowsheet or decisionmaking....

DR. CHILDRESS: Well, put up the one that in color we have.

DR. LO: And I would just say to Alta, I think, I like the idea of presumptions but if we are really concerned to protect or preventing the egregious cases, I think we can say that there are a set of circumstances which, if they are all present, it's mandatory. So I think if you're institutionalized, if the person who is the principal investigator is also a caregiver for you and if the nature of the research is such that it's not just a little more than minimal risk, it's substantially more, it's not a presumption, it's mandatory. Let me go back to the original question which was people with less than minimal risk, do we want a formal assessment of capacity? And I guess I'm maybe having trouble with understanding what people are really thinking about. As I understand things, if you really were concerned, probably the most extensively studied and best validated instruments is the MacCarther instrument. I know that Eric doesn't like this, there's a lot of criticism but that's the, I think, the best thing out there going. There are other ways of asking questions which are not quite as lengthy which probably, it seems to me, do the job as the screening instrument. I think appropriate is fine because it covers a lot of ground and it seems to me that the amount of attention you put in up front has to do with the research circumstances, and then what usually happens, as little red flags start going up as you answer a brief screen instrument, you say whoa, this is really much more serious than it first appeared, and now we have to do an even more formal, lengthy assessment. But to have everyone go through a long formal assessment from the onset, I think, it's sort of a cost- effectiveness question. So I agree with the principle that no one should be included in the study on the basis of without consent. But how it measures the efforts you make to really determine that seems to me will vary with the situation, and including the initial responses you get when you first start to make the assessment.

DR. SHAPIRO: I think one of the problems we're having with this Recommendation 3 is unlike the other recommendations, it has no text beside it at all and that has, I think, and that's—to look at the memo you'll see some text in there. I can't say I feel strongly on any of these issues. But my own view of this matter is that we ought to be putting teeth in our recommendation at the greater-than-minimal risk area. I am much readier to allow the presumptions to flow the other way in the less-than-minimal risk concerns. Try to make it, try to highlight in text the need to be thoughtful, careful. If Bernie were head of all the IRBs, I wouldn't need any regulations. We would all be in fine shape, but that's not the way life works out so on the less-than-minimal risk, excuse me, in the minimal risk research, I'm quite prepared to allow the presumptions to go myself. You let the IRBs use judgment, let them to presume the investigators know what they're doing in this area and so on and get consent in a normal way. This doesn't eliminate the need to get consent, but when it gets to the greater than minimal risk, I do think we need to bring something like a more formalized assessment into play. And I know we don't, and one of the problems here and why we can't use words like validate is we don't have any really validated ones yet. And so we just have to mobilize people's best attention to the problem as opposed to, say, do this test or do that test because we

don't have any yet. And in some sense, the issue about independence has been argued back and forth a lot. That's out there in the literature and you'll see a lot of it. In some sense, if there weren't conflicts of interest, a qualified professional would be enough to say, right? Someone who is qualified will do things that their profession requires them to do and so on. The cutting edge is the that the course that we're on runs right into the conflict of interest question, which is what so much of this is all about. So I'd be very interested to know where the committee feels on that issue. Bernie raised it and I think if we just focus on it for a moment now without trying to complicate it with other issues as to whether the independence is critical to this now in the greater than minimal research—I'd just like to know how people feel about it so we can move ahead. Eric.

DR. CASSELL: I think that's what makes it what it is. The minute you don't put independent in, then we're back to the simple thing. Somebody on the team said he was okay and that's okay. I don't, I think independent is necessary.

DR. SHAPIRO: Okay, how do others, other people feel?

DR. SHAPIRO: Let's just take a straw vote and then we have to start moving forward. How many really want us to stick with independence? Okay, that's clearly the majority of the people here. So that, again, I want to remind you what Jim had said before. If there are issues which individual members here feel very strongly about as we get to the end of this report, there will be an opportunity for people to express themselves in that, in this or any other conference. Let's assume that the independent, I like Alex's wording—acts as qualified professional. I think it is much more helpful, I think, than "expert," and also widens the possibilities for an appropriate reason.

Professor Capron: What happened to Alta's suggestion vis-a-vis the presumption, because I thought she was raising that in response to Bernie's concerns?

DR. SHAPIRO: Let's go to them. if the language of the recommendation were to read something like "for research protocols that present greater than minimal risk to persons with mental disorders," the presumption is that investigators will employ an appropriate method, and then an IRB should approve a protocol when the presumption is not met only when persuasive grounds exist. We're dispensing with this means of assessing the subject's capacity. That's what you had in mind. Is that right?

Professor Capron: Right.

DR. SHAPIRO: I'm glad you—I meant to raise that. I'm glad you did. How do people feel about that issue so we'll know how to write the report?

DR. CASSELL: It allows them to exclude stable outpatients who have had no symptoms for a long period of time and something like that. Right. Is that what you mean?

Professor Capron: What the presumption is, and I thought that her language was responsive to Bernie's concern, that the person would say, okay, this is more than minimal risk but what it involves is x and that is a situation in which I will do a formal assessment but I shouldn't have to pay for an outside expert. And then the IRB would decide whether that was a persuasive ground for dispensing with that. But the presumption that they will be operating on is no. If it qualifies as more than minimal risk, you've got to do it. You've got to do this. Now, I, I just wanted to get this out on the table again. I'm, I'm still, I like the basic approach of this is what the IRB should do. But I understand Alta's alternative to allow what Steve was referring to as the element of judgment to come in when an IRB says, in terms of proportionality, this is overkill for this particular research although, yes, it is "more than minimal risk." Because, for example, in Bernie's example, it involves a questionnaire that has to do with drug use and we call that more than minimal risk, but we really think that you don't need an outside expert. In other words, we are comfortable with the risk that someone would be enrolled in this who doesn't actually have the capacity that the investigator says they have.

DR. CHILDRESS: Go ahead, Alta. Then I know Larry's going to have to leave in just a few minutes. We want to get his final word.

MS. CHARO: I'd like to emphasize that my purpose of proposing this was not, in fact, to make it easier to enroll people in protocols that wouldn't qualify as a minor increment over minimal risk. So that is not the scenario I had in mind, actually. My purpose was in allowing IRBs to exercise judgment where they thought that a capacity assessment could be made by something less strenuous than a formal independent assessment instrument, and that would be what you were suggesting. Somebody's been stable for a long time. I was not hoping to see this used as a way for IRBs to differentiate among levels of risk in the category of more-than-minimal. I wanted it to be used as a way for them to not need to go through all these hoops where, despite the fact that the subject meets the technical description of a population at risk of impaired capacity, it's nonetheless quite straightforward to tell if they are competent or incompetent without all of this rigamarole.

Professor Capron: That kind of language, however, would in the end give flexibility for either?

MS. CHARO: No, I guess actually we'd want to change your suggested wording a little bit so that there's a presumption that they'd have an independent expert unless there's persuasive evidence shown that the capacity assessment can be achieved, can be reliably achieved without those needs.

DR. CHILDRESS: Your comments focused more on the independent assessor, and that's one I would go in the direction that Bernie suggested—if you're institutionalized a whole host of factors could play a role there. We might want to pull

out the independence and distinguish that from the formal assessment. And your comments focus much more on the independence.

MS. CHARO: That was only incidentally, of course, I mean.

DR. CHILDRESS: But it seems to me that one actually could make a plausible case for that, and requiring the independence might be circumstance-dependent.

DR. SHAPIRO: So we have just decided that we liked the independence? Right? And so I think we ought to require that.

DR. CHILDRESS: But you're opening up the door for the presumption. That's what we're dealing with here because there's ways to set presumptions that have to do with certain kinds of circumstances.

DR. SHAPIRO: If I understood what, not focusing on language, we could generate the language. But if I understood what Alta was saying was that yes, this is fine, but as the normal presumption about the way the IRB would operate and investigators would behave or would be required to behave. However, and leaving open the fact that we can anticipate and articulate all the various kind of issues that come up and the scenarios that come up and so on and leave it open for the IRB to not use this recommendation.

DR. CHILDRESS: But as we've heard several times, if we go that way and can't give any concrete examples, can't give any real meat to what we might considered a persuasive grounds for not following the presumption then I think our report basically at that point...

MS. CHARO: Here's the example I'm keeping in mind with Eric's help, okay? You've got somebody with schizophrenia, so that's kind of a population that might fall into this "antennae go up" category. The research is more than minimal risk. And the presumption would be that you'd have to have an independent formal assessment of capacity to consent and the investigator says, I'm going to work with the population of people only who have been well controlled with no overt symptoms for over 2 years. And the research itself, although it's more than minimal risk, does not in any way alter their medical management in such a fashion as to threaten in any obvious way. Their continued stability. Therefore, I think it's okay if we, the investigators are to simply assess the person standing in front of us as competent to consent in the same way you'd assess anybody else as competent to consent without needing to bring in an independent expert. That's the kind of example I have in mind of an investigator coming back with a persuasive justification.

DR. CHILDRESS: And before we try to resolve this issue, I want to get Larry in but we'll come back, sorry Harold, we'll come back and actually decide whether they want to go the presumption route or the absolute requirement route. Larry, do you want to give some parting words on things we need to attend to?

DR. MIIKE: It's just that issue that I brought up in the beginning where we're looking at people with fluctuating capacity versus people with no capacity to give consent. I don't understand the logic of requiring that for those that fluctuate in capacity; the only time they can participate in research is if they consented while they were with the capacity. And yet in those without capacity we say for greater than minimal risk and would benefit, someone else could make a decision for them. And then the way that you dealt with the part where there is no benefit was to totally eliminate people without capacity to make decisions from participating in that research, where I would have preferred the other way, in which those with fluctuating capacity.... My understanding of the way you changed the 12 and 13, I believe, is that now those without capacity to consent cannot participate in any research with no benefit and greater than minimal risk. Isn't that right? In the revision of September 15th, I think you took that out.

DR. CHILDRESS: But it was replaced.

DR. MIIKE: I know but the way you split it off was that you eliminated that, that, maybe you haven't, but if that's still in there, then there is no difference between with benefit or without, right? But my point is that I don't understand you would allow research for people not capable of making decisions if someone else has the power to do that, and then only allow research for those with fluctuating capacity if they have indicated beforehand. I think that in the latter case, about people with fluctuating capacity, that you have to honor their wishes if they had made a specific request not to participate. But it doesn't make sense to me that that you say if they didn't give that permission, then under no circumstance could they participate.

DR. CHILDRESS: Point well noted. Okay, anything else you want?

DR. MIIKE: No, I mean those, there are lots of little things, but those were the parts that just logically, I couldn't understand the logic of them.

DR. CHILDRESS: All right. I think there are problems at that point that we have not yet fully worked out yet. Thank you.

DR. SHAPIRO: If you're not here this afternoon, we'll be conscious of your exhortation for us to get on with things.

DR. CHILDRESS: What I'd like for us to do if we could is to decide if we want to whether we want to go the presumption route or the absolute route now that we've already indicated that independence is an important standard for us.

DR. DUMAS: Are you talking about doing that now?

DR. CHILDRESS: Well, if you would get your comments in here now.

DR. DUMAS: Well, I've kind of lost track of the recommendations, and at one time we had a recommendation that in cases where there was more than minimal risk and

no benefit to the person, that we would not, we don't think that they should be involved in the research. Now did that change?

DR. CHILDRESS: We've got the conditions for that and a that we have to come back to.

DR. DUMAS: So now they can be involved.

DR. CHILDRESS: Right. We'll get to those later. And we've spent a lot of time on this particular one but I think it's a very important one; again, it's one that we got a lot of public comment on.

DR. DUMAS: That's, I want to just for the record, the main thing, the position I've had all along. I don't think they should be involved in the research.

DR. CHILDRESS: Will you be here for the rest of the day?

DR. DUMAS: No. I'm going to have to leave early.

DR. CHILDRESS: Are you leaving before lunch?

DR. DUMAS: I'm leaving now.

DR. CHILDRESS: Oh, you're leaving now, too. Okay. Anything else? Sorry I wasn't aware of that. I was aware of Larry's departure.

DR. DUMAS: I'm sorry. I didn't tell you but I told Eric.

DR. CHILDRESS: Okay. Anything else you'd like to make sure we that we attend to in this discussion?

DR. DUMAS: No, I think most of the things that I have had in mind about review, that's been one that has been on again, off again, and one that I feel very strongly about.

DR. CHILDRESS: Good. Okay.

DR. SHAPIRO: Jim, we're going to have to, Eric has a comment and we'll have to take that, but then you have public comments scheduled.

DR. CASSELL: We're on the issue of presumption at the moment right? And we have two alternatives. One is you can't get out of it no matter what and the other is there may be certain circumstances where the presumption is that the person has capacity because of a clinical situation. And, in other words, we could, the IRB could determine that if this particular population, although it is made up of persons who may, because of their disorder have decisional incapacity. The characteristics at this time suggest that they will not have decisional incapacity and therefore the IRB does not have to apply this test. That's one way to do it. Then the other way to do it is that it doesn't matter. Now I'm trying to think of the study and I think the example given of the questionnaire about

drug usage is a good one. That would be more-than-minimal risk, but here's the population that is out in the outpatient setting and the question is, are they using drugs? Do they have to, does everybody there have to be brought in and asked do they know who the President is and etcetera, you know.

DR. CHILDRESS: And by an independent...

DR. CASSELL: I'd have trouble with that. I must say. I got hard-nosed about all of this because I also live in hospitals and know about all of this stuff. But this does go a little far. So I think that the IRB ought to be able to release them from the requirement that the presumption in a particular population at a particular time is that they have capacity.

DR. SHAPIRO: Okay. Do people want to talk anymore or feel like talking about the presumption issue? Because if we could take a kind of straw vote on that now, we can, and then go directly to public comments if not. Let's just see how many are convinced by Eric's or anyone else's comments. Alta's—and we'll worry about language at a subsequent moment—that we should build in some leeway here, really, however. How many people feel that's a plus?

PUBLIC TESTIMONY

DR. SHAPIRO: All right. Well that's obviously unanimous. All right. And we'll have to leave that now and go to the public comments. People have signed up and I want to make sure we don't keep them here longer than necessary. Okay. We have three individuals who have signed up for public comment. I just want to remind all of those who will be participating that the rules of the Committee are five minutes; when you get to five minutes, I'll try to remind you, and then please bring your comments to a close. First is Ms. Marcia Pines from Baltimore, Maryland. Ms. Pines, are you here? Thank you very much. Thank you for coming today.

MS. PINES: Thank you very much, Dr. Shapiro, Dr. Childress, and Dr. Meslin, members of the Commission. I am Marcia Pines from Baltimore. I'm pleased to have this opportunity and I don't know if I'm going to speak for three minutes or five minutes but you'll give me the clue and if I could speak longer, I have other comments. I am the mother of a 50-year-old woman who has been severely disabled with mental illness since she was 17. I was a senior staff member of the Johns Hopkins School of Hygiene and Public Health, where I spent 22 years directing the IRB. I retired in 1989 but I am still very much involved in public policy. I attended the meetings of the previous two commissions, which studied and made important recommendations to Federal government on biomedical research policies and standards. In my capacity as director of the Committee on Human Volunteers at Johns Hopkins School of Public Health, I've prepared the policies and procedures under which the committee functioned. These

became the standard for the university back in the early 70s. After many years of working with outstanding people like Charles McCarthy, then director of OPRR, and others, I have been there, I've done that, and I had grassroots experience in reviewing research protocols on almost every detail for ethical issues regarding appropriate language, procedures obtaining informed consent as well as protecting the confidentiality of research subjects and weighing the risks and benefits in research protocols which came before our distinguished Johns Hopkins School of Public Health IRB. As a parent of a person with severe mental illness, or brain disorder, as we say today, I've also had great experience. Our daughter had her first hospitalization in 1968 at one of the most prestigious private hospitals, where she spent 19 months. And we as parents received no information regarding her diagnosis. Out of frustration we sought the consultation of a prominent psychiatrist from Johns Hopkins and heard for the first time that our daughter had schizophrenia, and were jolted into the realization that the rest of our daughter's life would be paved with peaks and valleys. Unfortunately, the valleys have overtaken the best part of her life. However, through this journey, Ellen was invited to participate in a research program at the Maryland Psychiatric Research Center. She agreed; my husband and I agreed. She had suffered for so many years with devastating illness that we felt that through research, perhaps we could find an answer to her misery and if not, perhaps it would provide answers for future generations. Our experience with the Maryland Psychiatric Research Center was excellent. Ellen received excellent care from a competent and caring staff. She and we were kept well informed at every step of her involvement in each new protocol. And as family, we attended family meetings, which were held as a group. We were being well informed by the inpatient director and other staff about current research protocols as well as new breakthroughs in clinical research on brain disorder. These meetings provided me with a foundation of knowledge that could have never been exceeded if I attended medical school in those days. Although, I must add, that after joining the Alliance for the Mentally Ill, I had the benefit of learning a great deal from other professionals around the country and from researchers at NIMH. So as family members, we've become very well educated in this field. I know you have heard from several individuals who have had other experiences with family members who have been involved in research, but I think it is important to understand that we as families must realize that our loved ones are suffering with a serious brain illness for which there is little known, and only through research are we going to open the gates of knowledge. We must be certain that every line of protection for these folks is in place. But at the same time, we must not impede the progress of research nor limit or discourage investigators into new horizons. There's a serious flaw in a system when accusations can be made, I should say unchallenged accusations can be made, by families, but the researchers are bound by confidentiality and thus are unable to respond to their accusers. I commend the Commission for the time you have taken to study this issue and to listen to testimony. I have reviewed the proposed recommendations and acknowledge the staff for listening and responding to comments, which have been submitted by many knowledgeable and experienced people. I would hope that this

Commission does not propose an infrastructure for institutional IRBs which will make it so difficult to approve valuable research. It is clearly necessary to build in protections for research in all brain disorders. In fact, for all clinical research. But we must not throw the baby out with the bath water. As a member of the NIH panel, which met last December to consider the IRB role in reviewing research with people with diminished capacity, I know the thought and the considerations which went into this final report, which I know you are considering. In closing, I want to relay a comment that I heard only yesterday from one of the prominent AIDS researchers at Johns Hopkins. Unfortunately, I was there for a very sad memorial for Jonathan and Mary Lou Clemonsman who are like our family. This researcher said to me, “Marcia, you can not believe how difficult it is to get a protocol approved these days. There are so many obstacles, so many hoops to go through, and valuable research requiring approval from the JHU IRB, the NIH IRB, the CDC IRB and then other collaborating institutional IRBs has caused over a year’s delay in furthering our studies in Africa. And then I received a letter in the mail yesterday from the Institute of Medicine stating that there is a serious decline in research protocols. I don’t know how much time I have sir, but, I think, I’m up?”

DR. SHAPIRO: Your time is up so if you could draw your comments to a close, I would appreciate it.

MS. PINES: Well, as you explore this critical subject, please do not allow the voices of a few to impede the process going forward. Please do not let us turn the clock back. I would implore that the guidelines for more education is critical. Guidelines for educating IRBs. Guidelines for educating researchers. And, I’m sorry I don’t have more time because I would like to comment on the item number 3 but I can write you comments. Thank you for the time.

DR. SHAPIRO: Thank you very much for being here today and we would welcome any other written comments you have and we would distribute them to the entire Commission. So you’re welcome to submit any further comments you would like. The next person on our list is Ms. Irene Lynch, from Colt’s Neck, New Jersey. Ms. Lynch, thank you for coming today.

MS. LYNCH: Good morning. I would like to thank the distinguished members of this Commission for the chance to give testimony today. I’m Irene Lynch from Colt’s Neck, New Jersey. In light of the current frenzy in the national capital, it is refreshing to be here. I see this as government at its best. I come to you as an expert witness. I am an ex-mental patient. The mother of six mental patients and the wife of another. I have participated in field work, as a field worker in several research projects about mental patients. I currently work tirelessly as an advocate for mental patients, most often without pay, as do many of the thousands of mental patients with whom I work and share the stories of our lives. To have been a mental patient and to have recovered is a growth experience; is a journey through hell and back. It is an uneven path fraught with emotional distortions and extremes and yet with a painful awareness of the depths of

what we do to one another in the name of treatment, a word for which I prefer to substitute the word control. But interspersed with these elements of fear, anger, humiliation, understandings, and isolation are moments of insight into the very best of human nature and how we could help one another. We have carried our knowledge into the self-help movement, which has grown tremendously with our interconnectedness, now worldwide through the Internet. We are historically, as you well know, an impoverished population and e-mail is affordable. The Executive Order that gives you your mandate states that government departments and agencies shall review the protections of rights and the welfare of human research subjects, and I note the very use of the word subject was an issue for this panel. It is difficult for me to understand how you can segregate someone and protect their rights and welfare at the same time, particularly when you deem them lacking in decisionmaking capacity. My concerns are these. The real nature of what society terms mental illness. The proliferation ad nauseam of labels known as diagnoses, especially as they relate to our children. The high use of doses of drugs at the onset of emotional distress and the combining of chemicals without a clear knowledge of their interactions with one another or their interactions with other environmental elements. The treating of symptoms instead of looking for causes. The misdiagnosis of mental illness in cases of the presence of infectious diseases, and lastly, the gross negligence of the medical professions in treating the many and varied physical problems of mental patients. All of which leads to my recommendations to you. That you seriously consider as human beings, you individually, that the basic assumptions of much of today's research involving persons with mental disorders is faulty. That the emphasis ought to be on wellness and recovery, not on bean counting beds; not on outcomes fashioned by managed care to cut costs; not on changing the chemistry of human beings, refashioning their behaviors, leveling the differences that makes some folks uncomfortable but which differences are really an important part of who the person is. That you'd include ex-mental patients in your deliberations, especially requesting that they sit with this body and that sufficient numbers of mental patients' experts determine the research protocols and the accountability thereof. I sincerely hope that this Commission will be instrumental in ameliorating the lives of some very wonderful people. I thank you.

DR. SHAPIRO: Thank you and thank you very much for coming here today to share your thoughts with us. Next, let's hear from Dr. David Shore. Dr. Shore.

DR. SHORE: Thank you very much. Having encouraged a number of investigators to read and respond to your draft during the July, shall we say, open season, and having seen a number of those responses to the draft and seeing some improvements, I certainly want to express my appreciation to the Commissioners and Executive Director for responding to many of the issues raised. I do, however, want to raise a couple of questions because there are several issues that have been discussed on which it is unclear to what extent the field is being heard and exactly what the Commission is saying. And rather than give a speech, I would like to simply ask four

questions and try to get some clarification about these issues because the people with whom I have previously spoken are going to ask me these questions when I get back to the office and I'd like to be able to try and answer them. First question. Would IRB waivers of informed consent for those with questionable capacity explicitly be allowed or forbidden? Yesterday afternoon, the group spent considerable time discussing the three major criteria for waiver of informed consent and I presume you would not have devoted that amount of time to that subject had you planned to throw it out the window. But, this morning, the discussion seemed to focus on the assumption that there will always be informed consent and I think it would be helpful if the group would explicitly say whether or not informed consent might be waived so that people would understand the implications of your recommendations of, in particular, for research deemed not greater than minimal risk. The second question has to do with an issue you discussed this morning. Would people with mental disorders, that is 20 percent of the American population currently, automatically be singled out as requiring competency evaluations? Clearly the discussions about more flexibility on that and perhaps rewording Recommendation 3, I think, would be welcomed. Number three, would studies be permitted comparing people who have one particular medical disorder comparing them with those who have another mental disorder? People who may be on similar medications, who may be in similar treatment environments, who may have similar degrees of impairment or, as I read the recommendations currently, could we only compare such individuals with healthy, non-mentally-impaired controls? As you probably know, there is a long history of research demonstrating differences between patients and healthy college students. That research has not gotten us very far because of the multiple confounders. And of course, I'm sympathetic to the desire to ensure that individuals with mental disorders are not exploited but, of course, distributive justice is already covered in 45 CFR 46. Final question. Will those who have progressive and gradually deteriorating disorders be allowed to have a surrogate enter them into studies that will be scientifically relevant when, several years down the line, that person does subsequently become incompetent, or will they only be permitted to agree to studies that are now relevant which in all likelihood be considerably less valuable by the time the individual would be likely to participate? Will legal proceedings be required even if the intervention to determine competency or a durable power of attorney is more traumatic and time consuming than the research intervention itself? Those are my four questions.

DR. SHAPIRO: Thank you very much for your questions. We will not respond to them all at this time. Some of these will be taken up this afternoon but we will certainly respond to all of them directly to you over the next few days. Thank you very much. The final person I have here today is Michael Sesco from the Citizens for Responsible Care. Thank you very much for coming this morning.

MR. SESCO: Thank you. Yes, my name is Michael Sesco and I guess my background is that I've worked a lot in the field and at psychiatric halfway houses. I now presently, I'm an outreach worker with homeless people so I'm very much in the

trenches. I edited a book taking first-hand stories from people who actually had been on the streets or in psychiatric hospitals, vulnerable populations. Many years ago I had my own experience of being in a psych hospital but wasn't treated with the aggressive sort of heroic treatments of neuroleptic drugs and allowed to go through the experience. So I come with that sort of background, in the trenches with very high antennae, if you will. I guess I come today because I had given some written testimony to the Commission, I'm not sure whether people have the time to read it so I came all the way from Baltimore to give you a sense of where I'm coming from. I think that most people who are actually in the trenches working firsthand with these people, not as researchers, and the actual people who are of these vulnerable populations would be very suspect or very wary of any aggressive sort of treatment that's sort of in the neuroleptic line. Which a lot of this research is, if not shock treatment or psychosurgery, which has come back. These are very strong treatments. People who have been through this stage of vulnerability are very fragile and it's hard to imagine unless you've been through this type of process, the impact of these types of treatments. So it's in that context that I come with, you know, very high antennae, very much awareness. One particular issue I think is egregious is that most people would recognize that it is a problem are the psychiatric challenge studies where the profession, these are federally funded researchers, are actually inducing psychiatric illness in order to make discovery and gather exploratory data. They're giving PCP to induce psychosis with people in psychiatric hospitals. That's in, I have the cites on that if the people want it. They're inducing panic attacks in veterans in the veterans' hospitals. All of these studies. That's the end that we've come to and it's hard to believe; most people when I tell them they don't believe it, even some neuroscientists. Physicians are deeply disturbed when I tell them. Most people get a very visceral reaction. How have we come to this? Well, there's lots of reasons but before I go into those reasons, another thing that disturbs me in the discussion today is that the use of language. I'm a writer. We talk about minimal increase over minor risk and all these different phrases but what's a suicide, what's a real death? Those are real things and I grieve the death of friend who had been in the psych system. It's an enormous thing when somebody dies, takes their life and dies. This language doesn't capture it and I fear that this use of language lowers our antennae and gets us away from our heart and what's really happening at times. Why we come to this pass, where I think there's a historic erosion of the Nuremberg Code, enormous profits involved and the fear of dealing with the actual pain in people's lives. These treatments basically subdue people, basically tranquilizing. They used to be called heavy tranquilizers. They block receptors in the head. So we fear to deal with the real pain and the solution is to use drugs to stop it, use force to control it. We have a research subculture. Maybe somebody should study them, sort of people who want to be on the cutting edge of research that becomes the bleeding edge of research often. I think a type of scientific mania where to be a professional you have to have real low antennae and you become a success and publish the papers, but what happens to real people? Footnote. Does this all really work? Is the system very effective? I think when studies have been done and there have been few studies where they didn't

use these aggressive heroic treatments that are in our contemporary culture here. Where they've just provided healing homes, let people express the pain in a safe environment. Their rates of success have been very much higher than when using these other types of treatments. I can refer to the Agnew double-blind study by John Ware Perry. There are a number of such studies. They've only been allowed in an isolated instances and because it's not politically in the mainstream. So that's just my overview. It's hard to do in five minutes but it's a little bit. There's another whole universe out there aside from this one that you need to sometimes examine your assumptions. I would end with simply a question that's somewhat rhetorical but it's a serious one. If we've had a five-year moratorium on cloning to protect potential life, why can't we do a five-year moratorium on psychiatric challenge studies that actually induce the illnesses that the profession has said to not want to, to want to stop or to deal with. Why can't we protect people who are living? Thank you.

DR. SHAPIRO: Thank you very much and as I've said to others, if there are other things that you'd like to share with us, you could put into writing and we would be glad to look at them carefully and distribute them to all members of the Commission. Well that brings an end to our public comment session today.

Professor Capron: In line with the public comment in distribution of writing, we had at our place this morning a statement from Robert Aller, previously here, when we were in Los Angeles, I gather, and maybe he also came when we were one time in Washington. I don't remember the times that he has been there. But he raises a number of points about our report and one question about a point on which he is, I think, suggesting we will be criticized in alliance among our consultants, on people who had financial conflicts of interest and I wonder whether this was something which you, Mr. Chairman, was aware of and you can reassure us that this was taken into account in obtaining or using their information. And as a more general question, whether we have in place a method which will inform us. I mean a conflict of interest is not necessarily disqualified in there's somebody we have some reason we should turn to. But, I guess as a Commissioner, I would like to know about it rather than learning about after the fact where I do think we're sort of open as an ethics commission to a concern that something is going on and the wool's been pulled over our eyes.

DR. SHAPIRO: I've not read this yet, so I can't answer anything specific with respect to this but be glad to do so later today after I have a chance to look at it. But we do attempt to look at those issues and consider them when we hire people and I don't know if we've had all the information or not. I just can't answer that question right now but I'll ask the staff about that and report back. Yes, Eric.

DR. CASSELL: In the public comment, I don't remember the gentleman's name but the question about waiving informed consent. I think it should be made as though that was also true, that also might be true in this category of research. So it ought to be

made perfectly clear that occurred in the research on tissue sample situations that are bearing no resemblance whatsoever to research on living subjects.

DR. CHILDRESS: That is something we will be considering in the lower right-hand box. It is something we have to talk about in this context for minimal-risk research. That will come up this afternoon.

DR. SHAPIRO: Well, it's not quite twelve yet but we're going to adjourn in any case. Please everyone try to be back here at one o'clock.

**DISCUSSION CONTINUES ON RESEARCH INVOLVING PERSONS
WITH MENTAL DISORDERS THAT MAY AFFECT
DECISIONMAKING CAPACITY**

DR. SHAPIRO: Assessment of people's logistic arrangements leads me to believe that although I've apologized twice about the fact that I have to leave at 2:30, I don't know if anyone else is going to be left here. A number of people have to leave by 3:00, so I think that we're going to have to move on as quickly as we can because once we get below a certain number it's really not helpful to make any major decisions. As a result, I have suggested to Jim or he suggested to me, I can't remember which, that we focus our attention now not on 4 thru 8, which are issues, not to say there are no issues there, but begin by focusing on material that begins on 150 with research that presents greater than minimal risk and so on. That set of recommendations which Larry was concerned with, as was Rhetaugh and so, Chairman, if you could get us started on page 150, which is Recommendation 9, we could perhaps go through that set of recommendations in which the memo you received contains quite a bit of information. That would be helpful. Jim.

DR. CHILDRESS: Let's, everyone should turn to that. We'll consider Recommendations 9 thru 11. And look back at, looking back at a draft for a minute, there's one important point on page 2 of our memo of 9/15 that refers to something, at the very end of that section and I'll just mention it now as to how the consent is to be honored. The important parts to focus on here, concerns have already been raised by Alta and others, Larry and Rhetaugh, about this particular one and then the set of recommendations that follow the next heading of "greater-than-minimal-risk and no prospect of direct benefit to the subject." And this will, I think, bring together some of the things we've already talked about but now will force us to focus the discussion very very sharply. So let's go into this and, Alta, do you want, well first let's see if there's anything about number 9, recommendation number 9 that people would like to raise. Questions have been raised about number 10 but anything about number 9?

DR. SHAPIRO: Comments, questions, concerns with step 9? Good, let's go on.

DR. CHILDRESS: Alta, would you like to raise your issue which overlaps with some of the others that have already left?

Professor Charo: Recommendation 10 concerns, to coin a loose phrase, therapeutic, greater-than-minimal-risk research. My understanding of the policy that we have been adopting up until now is that therapeutic, greater-than-minimal-risk research would be allowed to continue if the subject could consent or if an appropriate third party could consent. Right? And the appropriate third party was one, in fact, that generally we've been talking about very loosely in the same way that we talk, whoever makes the clinical decisions for that incapacitated person could make these research decisions. And it was all because there was a therapeutic component here. When I read Recommendation 10 as it's written, however, it's far narrower than that and would shut down a great deal of this category of research as written. As stated, somebody who is currently incapable or is likely to become incapable could only be used in research if three conditions were all met. And they were most pertinent that when previously competent, this person had expressed an agreement to participate in research through one of these durable power of attorney documents. Now, that was different from what I understood. It's a tremendous limitation because very few people execute durable powers even for clinical care. The chance they're going to do it for research is even more remote and I understood that kind of advance planning to be something we thought as essential in non-therapeutic research, but I was surprised to find it showing up here. And I wasn't sure, and this is inconsistent with the way the chart that's on the screen and that is in the appendix presents the decision points. That chart would suggest that all you need for an incapable subject faced with a choice of therapeutic risky research is approval by an appropriate third party. So, I wasn't, I wasn't sure which way we're trying to go anymore.

DR. SHAPIRO: Eric?

DR. MESLIN: Just very quickly and we, in discussing this both with Jack Swartz and with Jonathan Moreno, who could not be here today, it was thought that the point that Alta made was exactly correct and perhaps a useful modification which we didn't put in this memo. We didn't want to keep burdening you with more detail in the memo and preferred having it brought up for discussion, is to in line 20 of the text that you have from the actual report, it would read something like the following. Decision about participation in research: have previously expressed a wish to participate or their agreement to participate, and delete the document, delete the instrument. Now that's just so for the purposes of the record, the expectation for this language is that it would not be dependent upon the completion of a very narrow instrument such as a durable power of attorney, but that there only be advance agreement, and that interpretation I have just provided is consistent with the overhead chart behind me, which perhaps the audience will also have available to them. Now the Commissioners may not feel that that's

appropriate but it was, again, a piece of drafting that was narrower than it had been intended.

DR. CHILDRESS: Let me just press that for a minute because it's not clear that the overhead actually does that; it goes a lot further than this does.

DR. MESLIN: I'm just trying to narrow it and come back to this.

DR. CHILDRESS: But if you build it, it's, I'm not sure, yeah that's exactly the problem, I think. And if you go the direction of the overhead, with the legally authorized representative's permission and no subject's consent, then you basically get rid of this stuff. That's where I think the concern is because it's so limiting. Now that it seems to me that we have to decide as a group if that's where we want to go. Other comments, Bernie?

DR. LO: Could I ask two questions first?

DR. CHILDRESS: I'm sorry, I'm sorry. I had told Eric I would come back to him first, I'm sorry.

DR. CASSELL: Well we now have two possible modifications. First of all, I think that Alta's basic point is absolutely correct. The question is, for me, does the subject have to have known about the research in advance? And would they, had they expressed some opinion about agreeing to that kind of research? And I lean to that. Although on the other hand, what do you have a legally authorized representative for if it's not to act on your best behalf?

DR. CHILDRESS: And whether is the prospect the right benefit?

DR. CASSELL: I'd like to hear something that would tell me that the subject doesn't have to have said, oh I think that's a good kind of research to do.

DR. CHILDRESS: Eric and then Laurie. I mean, Bernie. Sorry.

DR. LO: First a couple questions. Are we allowing this expression of preference to be oral or must it be written, and with what degree of documentation? And secondly, must the subject, while competent, have consented or agreed to this specific protocol or research of a certain ilk under which this now protocol falls? Again, that, those have tremendous have implications for how likely it is that the subject would be able to enroll in this kind of therapeutic, more-than-minimal-risk study.

MS. FLYNN: Just to follow up on on this point, I was wondering what kind of expression was going to be deemed acceptable and what degree of focus or specificity such an expression would need to have. Given that we're talking about research that is beneficial, that that's the role of the legally authorized representative, and unless there's some clear dissent or expression of a lack of support for participating, and given the lack of clarity about that what that expression looks like, I'm having trouble with it. It's also

just in the real world of practicality, highly unlikely that individuals who are this symptomatic or having this much difficulty in making decisions are going to have had the kind of discussions that would yield some kind of real clarity in the minds of those who would be reviewing this. That this particular kind of research was acceptable and such expression had been made. I think the cognitive impairments and the ongoing disability that often characterizes people with fluctuating capacity would likely have mitigated against their being able to make a statement or express a wish that would be actually be useful.

DR. CHILDRESS: Tom.

DR. MURRAY: Laurie said much of what I wish to say. If someone has expressed a prior wish not to be involved in research, I think that's dispositive and would probably say that in the recommendation. If on the other hand, as is more likely the case, someone has made no expression, then I would leave it up to the legally authorized representative, where in these cases, there is some possibility. Is that consistent with yours?

MS. FLYNN: Yes.

DR. CHILDRESS: I have Alta, Trish and then Steve.

Professor Charo: I, too, would like to argue for a situation in which a person's surrogate, legally authorized representative, is given a free hand here in this one category. Absent express wish not to participate. First, everything having to do with advanced planning has been nightmarish because it has all the problems of informed consent exponentially increased by the uncertainties of what that consent means and what they're consenting to over the course of years of unknown developments. I don't like that business to begin with, but it's been a kind of necessary evil in the non-therapeutic area. I don't like it whether written or oral in its form of advanced planning. The second is that this is consistent with the way in which we've been approaching other situations with decisional impairments. Again, let me refer us to the example of research in an emergency context, where routinely if there's somebody in the car who is a family member of the person who is now bleeding and lying on the ground, they've been allowed to make decisions to go ahead and try an experimental procedure if it were therapeutic, it had potential for some kind of therapeutic value. The controversy there that unconsented research was where there was no surrogate decisionmaker at all. And, third and finally, this is a particular population, and here I am referring to specifically those that are mentally ill, where there are very frequent drug trials looking at various variations in dosages, variations in administration, administration protocols, minor variations in drug formulations looking to tweak these drugs to make them work. Because you're working in the drug area, it's very unlikely you're going to meet the minimal risk definition, but it is also very likely that the reason that people are going to be enrolled by their surrogates is because their current treatment is quite imperfect. It's

not that there's no therapeutic option, but it's quite imperfect. And if we insist on some degree of advanced planning, an unrealistic expectation, we will, I think, very much shut down not only biological new research but a valuable source of potential improvement for these people.

DR. CHILDRESS: I have Trish, Steve and Harold and Bernie.

MS. BACKLAR: I just want to ascertain the fact that when we talk here in Recommendation 10 and we said the potential subjects previously incapable of making decisions about participation in research have previously expressed their agreement to participate, and we are agreeing that legally authorized representatives may do that for them if they don't have capacity at this particular point. That they will have actually appointed that person, that this is not somebody who will have been appointed for them.

DR. CHILDRESS: Which makes it even more restrictive then. In this case it goes the opposite direction from the comments to this point.

Professor Charo: A legally authorized representative is not necessarily somebody who has been appointed.

DR. CHILDRESS: And as we have been using the term in the rest of this document.

MS. BACKLAR: At this point, if these people have agreed to be in research and they haven't agreed to be in research, we're saying they've agreed.

DR. MURRAY: They haven't said "I don't want to be involved in research," and they have a legally authorized representative that says that given this trial which may confer some benefit, possibility of benefit, we leave it up to the legally authorized representative to say under these circumstances I will consent on behalf of my....

MS. BACKLAR: Well, I would like to say I'm very concerned about people being put into research in which they haven't made any kind of choice at all other than that they're not, that they haven't made a dissent and that they haven't appointed somebody that they would, who would be there to make that representation for them. That is what I'm trying to say.

MR. HOLTZMAN: So summarizing, a number of people around the table are effectively saying that 10 should read the same as 11. Trish is expressing a dissent to that. And the key distinction between the two is whether or not there has to be an expositive expression of agreement prior, and it's an implication of the way this is written that that prior expression would have been made to a legally authorized representative who is appointed prior. Okay.

DR. SHAPIRO: I'm just asking for some help from some of the Commissioners who will understand this area better than I do. As I look at this and ask about planning and not planning and so on and obviously if you eliminate the planning part of this, it

simplifies the whole thing a lot and then you don't have to worry about what they agreed to exactly. Is it the nature of the research or the risks, or, it makes everything a lot simpler that's certainly true. But I need some help with this. I think of some conditions where people have fluctuating capacity, where large parts of their life are spent, fortunately for them, in conditions which are really quite normal, if I could use such a word, of where they are perfectly capable, put it that way. And parts of their life are not and it's, I understand, not easy to predict when these things occur. But for a person in that capacity, in that condition, it's a little bit hard for me to say when they're not well, someone they don't know, never heard of, could be the State, could be someone from an IRB, could sort of contribute them to this. Now I need some help with that because I don't think that anyone really believes that or is suggesting that, but maybe we are but that's what this would seem to say. Because we talk about people right here who are fluctuating, I mean that's one of the categories. How should I think through that problem?

DR. CHILDRESS: Controls would be at the point of how one understands "legally authorized representative" in the state and institution.

Professor Charo: Exactly. There are two things here. First, who is this person who's suddenly being given the power to enroll somebody? It's not the IRB and it's not the State, it's by custom or law, depending on where you are, it's a series of members of the family and on rare occasions close friends. Few States do that, so it's a fairly narrow circle. Now on what basis are they supposed to go ahead and enroll somebody? And there was some discussion about this at the public comment and in subsequent memos from the staff, and I wondered if that might be the origin of this particular change here. There's a very rich literature about how it is that third parties should exercise the ability to choose for others, and the best kind of generalized wisdom here, and maybe Jim will give it more detail, is that they should start by trying to figure out what the person would do for himself if he could. And that there is a genuine duty to figure out, if you can, what they would do. And in that quest to figure out what they would do, you're allowed to assume that most people act in their self-interest, so they try to protect themselves from harm. They try to grab at benefit but you might know something special about this person that makes them deviate from the "typical." And if you really can't tell what that person would do, then the next best thing would be to act in what seems objectively to be their best interests. And it's on this basis that these third parties make clinical decisions all the time when people are impaired. And the question that faced us early on was whether we ought to use exactly the same standard that's used in clinical decisionmaking in the research context. And in general, the answer is no. Research is different but where there's a prospect of therapeutic benefit it was murkier. And if you're in a field, and this is actually one of the advantages in working only with a mentally ill population, if you're in a field where the current therapies are so imperfect that the prospect of benefit through research looms large, then it strengthens the argument that this is a circumstance where the standards for clinical decisionmaking with third parties

could apply in a very ethical fashion. But you have to be confident that the third parties will live up to their duties.

DR. CHILDRESS: Bernie, I suspect Trish will want to respond to this and then I have to propose that we actually move and so we can see where people stand on this particular one. Bernie.

DR. LO: Let me start out by saying that I support the idea of first of all making 10 and 11 consistent and certainly not making it harder for patients that tend to be enrolled in these types of studies than in 11. It seems to me that the reverse of protection you would want. So I agree with the thrust of what Alta was saying. With response to, in regard to what Harold said, again, I'd agree with Alta, that to the extent that we know what the patient would have wanted prior, through general statements or specific statements, the surrogate ought to follow those unless there's a compelling reason not to. You can't do that, you'd be substituting judgment based on everything I know about this person, what would he want me to, what would he decide in this situation? And if you say I just really can't tell, what do I as his surrogate think is best for him or her under the circumstances? And I think there's a caveat we need to put in saying that what empirical data we have leads us to doubt whether surrogates actually follow that sort of procedure. And so I think we need to put in here some text that's been there before about how it's important that the IRB make sure that the investigators put in the protocol a discussion with the surrogate that covers the points that it's not what you think you would want but it's what the patient, the subject would want. There are a couple minor points we I think we need to tidy up. One has to do with what we mean by legally authorized representative. And I think, Harold, your concern is, I take it, is that there's a guardianship procedure and someone, I once had a patient whose guardian was Wells Fargo Bank and the person who picked up the phone at Wells Fargo Bank to conserve the estate, to conserve to consent, leaves you very, may lead you to more trouble. So to the extent, the person who's the surrogate is not connected to the patient, doesn't know the patient, doesn't know what the patient would want and has no kind of ongoing ties of affection, responsibility and stuff, this starts to fall apart. Then the other point is, I agree with Alta totally, that there are going to be very, very few patients who fill out a research advance directive, but to the extent that someone takes the trouble to do that, I think that should probably be dispositive absent a really good reason. So I'd like to, my suggestion would be to make it an **or** rather than an **at**. That if you, in this type of research, either if you've given prior consent through an oral or written directive or if you haven't expressed dissent, the appropriate legally appointed surrogate makes the decision for you based on the standards Alta went through with the caveat that if at any time during this you object, you're withdrawn from the, at least that portion of the research.

DR. CHILDRESS: After Harold's comeback, we might even be able to come back and get some sense of the body on that direction. Harold.

DR. SHAPIRO: I want to make a, it's not a suggestion. It's not well enough thought out to be a suggestion. And I'm ready for someone to tell me to backspace after this and I'll forget I've even said it. If you just look ahead to Recommendation 11 which is, I guess, Steve pointed out, under certain circumstances 11 and say collapsed, which in itself is a nice, is a nice thing. I have always, I have always struggled over the word "never" in that recommendation because I had envisioned in my mind of someone who may have been ill thirty, forty, fifty years but not when they were born and so that never is always, I didn't ever know how to quite think about it and I began as this discussion is going on this afternoon, I began thinking of another way of describing that. That is someone who, where the current diagnosis is that they will never recover the decisional capacity. That could be a current. I don't know how to describe that well but I could imagine people in advanced Alzheimer's, other kinds of things where they will never, and in that case, 11 seems fine to me. It seems like there is no other choice. But I am still bothered by this case where someone will recover. The diagnosis is that they will before very long recover. They'll have episodes and so on, but that case still bothers me. Now I think what I've just said may make things more confused than helpful, I'm afraid.

MR. HOLTZMAN: No, I think. I was fascinated by your remark because what you were trying to get at was the sense that if someone had or periodically has sufficient capacity to exercise autonomy, the idea that someone else would take over that rule for you is troubling. You go to 11 and you say to yourself well, they never had so from, for many if not all things in their life they're having, many things in their life they're having to give that over to someone else. But at the next layer you should ask yourself, Harold, why shouldn't I be equally troubled there? Why does that difference make you feel okay about 11? I could read your argument about feeling uncomfortable with 10 leading to an 11 which prohibits....

DR. SHAPIRO: Well, I just, the image, which I'm not going to say this again because I'm willing to be guided by the rest of the Committee because I think I don't fully understand this well enough, but the image of someone who is waxing and waning, of them being volunteered so to speak when they're in one of their difficult periods rather than waiting until that episode is over and they are better and one could discuss matters with them is something that bothers me a little. I don't know quite how to take care of that concern.

DR. MURRAY: There's a factual presupposition in what Harold just said which Laurie, I take it, thinks is probably, as usually, incorrect based on your discussion before about people that would fall under current Recommendation 10, are usually, have significant impairments in other realms that it would make it unlikely that you'd have a long conversation with them about.

MS. FLYNN: It would be challenged, could be challenged. It's highly individual.

DR. MURRAY: But I have a different, I want to make a different kind of suggestion. It seems to me that it's not so much whether about how to combine 10 and 11. It's not so much whether somebody has never had the capacity to speak for themselves about their desire to participate or not. That's not important. What's important is do we have a statement on the record or a reasonably construed statement about their wishes with respect to them participating in research? That's what matters. Not whether they never could doesn't really matter. So you start with that. Do we have it or do we not? If they've said no at some point and we think it's pertinent to the research at issue, that's the end of it. That's really the answer. If they said yes, we're enthusiastic about it and we think its pertinent to the point of issue we may want to have other protections like the legally authorized representatives also consenting. We can say that and maybe we want to add a condition such that where someone's capacity to consent is fluctuating and where if it would wait, if we would wait a little bit, we could ask them and get a morally meaningful answer. We would probably, an IRB should consider that or we could advise IRBs to wait and not embrace the inclusion of such individuals in such studies when there is a reasonable capacity, where there is a likelihood within the near future that they can in fact answer for themselves.

DR. CASSELL: Well, I'm trying to think of the group that we're talking about. Here's a group of persons who's usual state around the time that we're talking about, sick enough, so their usual state includes decisional incapacity. They're sick and they're not getting better, which is one of the reasons why they're going to be enrolled in this particular protocol. If they don't come in within the next six months, they're out. That's it. Now, and everything from the past tells you that their usual state is not going to change. That is a thing that happens to people. There are groups of patients who are like that. The question is, you could make an argument for saying well that's the way it is. There's no research that could be done on them. We cannot really represent them without taking a chance of making a mistake, and we're precluded from doing research on them. On the other hand, to do that, I think, what would do harm to a group. The question is whether that harm is greater, the harm of not doing the research is a lesser harm than the harm of doing the research on the possibility that you're not truly representing them correctly. That's where we really are. Myself, I feel that there is such a thing as waxing and waning capacity and that you may not get this, that they won't be better soon. That's what their parents have been hoping for the last 23 years and they won't be better soon. And the question is do you just feel that they're exempt from research? How do you feel about that? Do you think they should be exempt from research? Remember their legally authorized representative, we can specify even more closely. Their legally authorized representative may be the parent that's been their caretaker all this time.

DR. SHAPIRO: I want to think about that a bit. I'm not sure how I feel.

DR. LO: Eric, I think, posed the question very well and I would just respond that I would be concerned that they'd be able to answer the question, is anything going to benefit this group of patients because we never been able to do the research on that group. I just wanted to say that you can't totally foreclose research on a group of patients on whom you have no good therapy at this point. That's, you want to be able to do the research in a responsible way. To go back to Harold's comments about waiting until you recover, I think where the nature of the study is that that is feasible, we should encourage that, but I'm thinking really of the therapeutic studies where you're trying a new drug that may in fact create some clinical fruit but you don't know until you test it. And so you can't really wait until they recover because you don't really expect them to recover. And fine, if we have to keep coming back to the idea even if someone never had, or doesn't had, excuse me, never expressed a preference about the research protocol or research in general, if they dissent from the actual study as you're carrying it out, that dissent is possible so that there is some protection for the preferences, whether they're autonomous of the subject, regardless of the consent that was given by the legally authorized surrogate.

DR. SHAPIRO: I think dissent, honoring dissent, of course, is extremely important and we've all said that all along. That's not controversial among us. You have to remember with the population which we are defining as to who might be on the subset of those. Part of them are decision-incapable. Certainly we have to honor dissent. We don't know if they are capable of knowing their best interests. I think that's a defense and a good one. We ought to keep it. I'm not sure how much, I know, I don't give a lot of benefit to it all and I'm glad we have it. If one looked at this Recommendation 10 and 11, which I'm trying now to see if we can't and if we talked simply about people who are currently incapable of a decision about participation and not worried about whether they have always been incapable or they at some future day be in some different status, because 9 already says when they are capable that we go ahead in the normal course of way and get informed consent in a normal way. And so what 10 and 11 are concerned perhaps with are people who are not currently capable and it doesn't matter how long they've been in that, and one could take the view it doesn't matter how long they've been in that condition. But during that period, if you put it that way, then you could go to something like 11 which says that their legally authorized representative can make the decision and what one has to worry about is that person or persons or class of persons that might qualify really do represent this person's best interest. And while I think I'm prepared to go ahead and go along with that, it is sobering sometimes some of the evidence that surrounds the way these people make decisions and whether they, you know, as the stuff we've read, they often make decisions they themselves would never volunteer for, even decisions that they think the person they represent wouldn't volunteer for. There's always this kind of evidence. It's not so comprehensive that we can rely on it, it's just sort of anecdote. Given the importance of continuing to do work

in this area for these people as a group and those fields as individuals and here there's a prospect of therapeutic benefit, I guess I would be willing to go along with that.

DR. CHILDRESS: And I think with the addition which I don't obviously have in the text, I think we'd do a better job with defining a legally authorized representative later with the material that Jack Swartz has added so some of this gets resolved a little bit later in the text. But, I, the point that's already been made that we really need to indicate here, the basis of the legally authorized representative's decision and actually give recommendations about what IRBs and investigators ought to be looking at in terms of the tier where you have the fluctuating and persons that express certain wishes and that sort of thing. That ought to be done and moving onto the best interest later. I have several who want to get in. I have Trish, Laurie, Alta and Tom. And then we may be at a point where we can actually take a straw vote.

MS. BACKLAR: So I would really like to ask a few questions actually. Are we proposing here to put people into research that's above minimal risk that they have neither consented to the research, putting away the dissent aspect, putting that on the side. So they have neither consented nor have they made a choice, a clear choice about this and they, and neither have they chosen to speak for them. Is that correct?

DR. MURRAY: You left out a condition Trish. Research that offers the prospect of direct benefit.

MS. BACKLAR: I just put that aside. I said more than minimal risk. You would have in order to persuade me, you'd have to show me the kinds of research that might occur where it would be okay for somebody to be in a research protocol in which they had no personal choice about this. I'm very concerned about this.

MR. HOLTZMAN: Well the example was given. Someone has a condition, they fulfill everything you've just described and now there's a new drug, right, so it's more than minimal risk, which is believed capable of treating that condition.

MS. FLYNN: It's vast numbers of people, Trish, who participated in the clozapine trials who were among the most ill of individuals with schizophrenia, many of whom were quite impaired for many years, for whom current standard therapies had very limited effect; who had not been truly capable of making those kinds of choices or even in some cases expressing those kinds of issues. Their surrogates in most cases were family members and those trials as we know have made an enormous difference in the quality of life and have encouraged even more to the point a whole new generation of clinical trials to come forward where we now have in schizophrenia a choice of 4 or 5 new neuroleptics where a decade ago we had none.

MS. BACKLAR: So in a sense you're saying what Alta is saying about this. Alta is saying about emergency room research with people with stroke who come into an emergency room in which there is nothing that can be done except to try something and

there's no adequate standard of therapy that's going to work for them unless you try something that is experimental. Is that correct? Is that what we're talking about?

Professor Charo: I think you're perhaps overstating it just slightly by saying that there's no standard therapy. The prospect of therapeutic benefit, and I mean therapeutic benefits because we haven't, excuse me I know I jumped, but we haven't highlighted the fact that we need to clarify that the benefit here is not money, it's not getting a chance to be in a new institute, right?

DR. CHILDRESS: It's one I've suggested e-mail messages having at every single point.

Professor Charo: That there's a therapeutic benefit that's possible through this research specifically because the experimental treatment offers the prospect of being better than existing treatment, even if existing treatments are not useless. So it's not quite as strong as what you said.

MS. BACKLAR: That's what this person, for instance as Laurie described it, the existing treatments may be useless because we have classes of people in this group and this particular population we're talking about, standard treatments do absolutely nothing.

Professor Charo: Sure, that's just an even more dramatic example.

MS. BACKLAR: We are suggesting this in a situation where the person's life at the moment is so bad that this will not make it worse and may improve it.

Professor Charo: It could make it worse. There's a risk.

DR. CASSELL: We don't know. They may have to. It may wipe their bone marrow out.

MS. BACKLAR: And so what kind, so what kind of safeguards would you, would you put in place by putting someone into a research protocol in which they have made no choices about this for themselves?

MS. FLYNN: They can dissent and their legally authorized representative presumably maintains contact, and if a such adverse circumstances are present presumably they are recontacted; one does have to trust that we do a good job of determining and defining a legally authorized representative.

DR. CHILDRESS: And I still have a list, I'll come back to these but letting people respond to Trish's questions here, I have Bernie and then I Alta responding to Trish.

DR. LO: You may have people who get therapeutic benefit with the current therapy but the side effects are intolerable and complicated. And the new drug *may* be a little more effective, but more importantly it's a lot more tolerable to the patient. So, that's another example. I would want to try and not exclude these people.

You asked a question I think is different than the consent question. There are problems with consent and I'll come back to suggestions for that—you're also pointing to issues of monitoring of what happens during the trial, which have nothing to do with whether—what kind of consent I get up front. It's the fact that—

MS. BACKLAR: I understand that. It's a double-barrel question.

DR. LO: Right. I'm saying that some of your concerns won't—will be addressed not through climbing up the initial enrollment process but making sure there's adequate protection later on when you get to it.

MS. BACKLAR: Okay. That's what I'm—what I'm saying. So, if you don't have consent I want to go the next step, which is what are you going to do to make sure that harm—further harm is not going to come to this person.

DR. SHAPIRO: We will come back when all this is done and look at the set of things we have, as Steve has pointed out more than once for the past few days.

MS. BACKLAR: For instance, I could not vote. I could not vote on the consent issue without having explored the other issues.

DR. CHILDRESS: Alta will respond. I'm going down the list and then we'll come back and get a straw vote on this.

Professor Charo: I think that the following four things at least are part of what keeps this from being abusive. And I say that as somebody who made this whole big thing about morally suspect. First is the fact that dissent will be acknowledged and will shut things down. Second is the narrow definition of "benefits." We're really talking about benefits flowing from exposure to the experimental intervention—the research intervention. Third is, I think appropriately, a narrowing of our understanding of legally authorized representative, in which we come to something that says whatever is legally authorized under State law is the outer limit of it but—no. Let me back up, sorry—that friends, and to the extent permitted by State—sorry—family and to the extent permitted by State law, friends can act as the legally authorized representative. But we're not looking for institutional. Your Wells Fargo example resonated. Fourth, Harold, that—as is done in other circumstances, at the first moment somebody regains their capacity to consent, they are reconsented. They are fresh—they're freshly approached and they're asked if they want to continue. That's routinely done now because, remember, we're narrowing a universe of things that are happening with third-party decisionmakers and good practice does that. And finally, it's not specifically protection, but I think it's a context we need to keep us in. Although it's true that as a rule, research interventions are going to be riskier than clinical interventions. I think we need to keep in mind that's not always the case. We comfortably allow third parties to make things efficient based on their best effort what people would do, in very risky clinical context, to make very big clinical decisions. But as soon as you put in as part of a systematic

investigation—alright?—we’re going to draw back from that and I want to simply urge that we not be knee-jerk about that because risk levels are not necessarily varying with whether something’s in a research context or a clinical context, although there is a large overlap. Right?

The bottom line is that in general we know empirically most people do not volunteer for nontherapeutic research, so it’s hard to say what a third party could legitimately say. I am guessing that this person would not want to be enrolled in nontherapeutic research. But’s it’s therapeutic research. We’ve seen lots of examples of people wanting to enroll, and it’s much easier to imagine a third party legitimately saying, “I guess he would want to be in this trial.”

DR. CASSELL: Can I clarify what she said?

DR. CHILDRESS: Okay. Clarification, right.

DR. CASSELL: The person has responded to treatment. They are now competent. And they—their first act is to stop their medication. They are now incompetent. What happens then?

DR. CHILDRESS: Alright. That’s a good casuistic case. And then I want to push to getting a straw vote after we get through these five comments. Bernie....

DR. LO: I want to go back again to Harold’s concern about a stranger surrogate making these decisions. I think you can put in that the IRB ought to put in some special monitoring of the consent by the surrogate in these situations and may want to have their consent monitored or something else to preclude these stranger surrogates who don’t know the patient at all and don’t have any ongoing relationship from consenting.

MS. BACKLAR: I think that you also, even if they’re not stranger surrogates, I think you need just as equally.

DR. LO: To make an optional additional protection....

DR. CHILDRESS: And I think a lot of things are emerging once we’re clear on which direction we’re going that can be helpfully added in both guidance and in the textual support for whatever we come up here. Some very important points have been made. Tom and then Carol and then Trish and then we’ll see if we can get a straw vote.

DR. MURRAY: Okay. Very quickly, I take it we are trying to function by the Bauhausian School of Commissioning; that is, only as complex as absolutely necessary to accomplish the task. So if we can go from Recommendation 10 and 11 to one recommendation that’s good, right? I think that’s where we’re headed. There will be cases where there’ll be no expression from the person about whether they want to be in research or not. And that’s what—we want to cover that. There’ll be cases where they say, “No, I don’t want to be,” and we think that ends the—ends the inquiry. There will be cases where they say, “Yes, I’m interested.” We want—I presume we want to take

that as the kind of information that the legally authorized representative ought to take into account, but not in and of itself as dispositive. Am I right about that? We already dealt with the dissent. I'm talking about where they say, "No, I think research would be cool." Do we agree?

Someone has expressed an interest in participating in research prior to...Do we take that as positive evidence that they ought to be enrolled in research? I don't think it would be rare that that would be the case. So it's relative information to whom? To the legally authorized representative.

DR. CHILDRESS: We're going to offer further guidance.

DR. MURRAY: Okay. Now, Harold had one other case that I'm not sure we responded to, and that is somebody who is wavering, do we today enroll them in the research, they're just not able to give us a meaningful answer. And Harold said it seemed to him an affront to say let somebody else say he can be in the research when if we waited a short interval and they could make up their own mind.

DR. SHAPIRO: I—well, I have been convinced by others that there's so much uncertainty in that case, and length of period often so long that we ought not to handle it within this recommendation. Although it did bother me, I'm satisfied, too, the way it's going. It doesn't quite feel that case, but that's fine.

DR. CHILDRESS: Eric Meslin's called my attention to something before I turn to Carol and Trish, that there are some materials earlier in the text—not in Chapter 6, in the recommendations. For example, on 104 and following "Protections to ensure that the LAR is an ethically valid surrogate for research decisionmaking." Now, in one sense it doesn't help to have it—it helps in effect there for certain purposes but what we need to do is go through in order to strengthen the kind of argument we're making now and pull out relevant summary points from that discussion to support what seems to be the direction that's emerging here and I appreciate Eric reminding me of this in the text. Do you want to add anything to that before I get to Carol?

DR. MESLIN: Carol [INAUDIBLE]? The only other thing is that we do mention on 106, and depicted up in the recommendations, that ongoing evaluation of LARs is an important issue, that there isn't enough evidence about their efficacy, so Commissioners may wish to revisit those pages as they continue to talk about the recommendation.

DR. GREIDER: I actually have a comment. I'm happy to wait until after the straw poll. It's not directly relevant to how we vote on this, but it's a comment about the text. It surrounds this whole area, and part of the issue is the box up there that reads "Does the research offer potential benefit to subject?" As the researcher thinking about experiments, it's very difficult for me to think about research having benefit if the research isn't completed yet. This whole issue about beneficial research—we've said it now a hundred times around this table today, and there is text on page 36 which deals

with this, and I would really like to see that incorporated here as well as previous Recommendation 8 that we skipped over. Bottom of page 148. I think some of that language needs to go in. I understand how people are using this term, but I think it's a very dangerous term because research means you don't know if it's therapeutic or not.

DR. CHILDRESS: So, in some cases—right, you don't know whether there's benefit, but you may be comparing two therapeutic agents, for instance.

DR. GREIDER: But you—a lot of this discussion is assuming that there's a benefit to the people getting those drugs.

DR. CASSELL: Potential. The intent of the research.

DR. CHILDRESS: The intent is to generate the generalizable knowledge, but you're doing it with therapeutic agents and thus offer the possibility of direct benefit to patients.

DR. MESLIN: I would just like to remind the Commission: We've had public comment on this, which drives to our attention the importance of this language, and the language that we crafted tries to track directly the language in the regulations which talks about research holding out the prospect of benefit. Now, a few Commissioners have been using the language of therapeutic benefit, and I think it would be important to state for the record that that's a shorthand expression for the much longer regulatory phrase, where research may hold out the prospect of direct benefit or the research does not hold out the prospect of direct benefit.

DR. GREIDER: I'd just like to see that reflected in the final text.

MS. BACKLAR: I'm looking at Alta's fifth point of what one might do in clinical treatment to try and help an individual with something that is hopefully going to be therapeutic. And I again want to point out the critical difference between the clinical treatment, where there is one person caring about one individual, one clinician looking at one individual in front of them, titrating things, trying quickly to make sure that something isn't going to go wrong if something looks like it's not doing so well; whereas when somebody is in a research protocol, it's not quite like that. There's not a clinician carefully focused on one individual. That individual is one of a group of individuals who is not being looked at and where the medication may not be titrated according to their particular needs because it's part of a group need. And, so, that is the danger area, and it ties in exactly with your point and so I'm still exceedingly uncomfortable about this. That's all.

DR. CHILDRESS: Maybe in the simplest form we should just see how people stand on basically combining 10 and 11, going in the direction of the legally authorized representative's permission with all the other conditions we mentioned, then providing in the text guidance, reference to empirical studies and the whole host of things we've talked about. So, how many are in favor of going in the direction of

combining—basically combining 10 and 11 into a recommendation about the legally authorized representative? Okay.

MS. BACKLAR: But that doesn't mean that we agree with it. If we're interested in combining it.

DR. CHILDRESS: We're going in the direction of the legally authorized representative model. That's what emerges. Okay. How many are opposed to that?

DR. CHILDRESS: Well, this is clearly going to have to be written up and we're going to have to find the justification. This was just the starting point to see if people agree with that direction and then we have a lot of work to do on it. Steve....

MR. HOLTZMAN: Trish just raised some very persuasive argument about the difference between the clinical setting and the research setting, even with therapeutic or potentially therapeutic agents. I don't personally remember a lot of discussion or any in this text sort of reflecting that kind of distinction. Is there?

MS. BACKLAR: A little bit...mostly reference to Applebaum's therapeutic....

MR. HOLTZMAN: I'm not that familiar with the literature, but what I found was that was a nice explication of when one is thinking through the prospect for—what's the language: prospect for benefit. That—sort of elucidating that a little bit, drawing that out. That just because it's a drug agent doesn't mean that the prospect is as great there as it would be if the individual physician is working with you on an off-label use and titrating, etc., etc.

DR. CHILDRESS: Nor does it mean it's less.

DR. SHAPIRO: It's really just a special example of a case why there are more conflicts buzzing in the research arena than there are in the clinical arena. That's just an example.

DR. CHILDRESS: It's a double agency problem here.

MS. BACKLAR: And a perfect example of this is this extraordinarily important medication that Laurie alluded to, which was clozapine, which my own son now is very successfully having a good life with. But people in that research protocol actually died, and if that had been my son that had died instead of his benefit now, which he did on other people's deaths, make one somewhat concerned. So that one person's death—many people may have succeeded and had a good life out of it. That one person—I'm concerned about that individual.

DR. CHILDRESS: Bernie, and then we'll move onto the next recommendation.

DR. LO: There's another side of this issue. I mean, I agree the double agency problem for principal investigators who are also doctors or patients—it's a big one. But, on the other hand, good research protocols that do drug studies have visits that are fairly

frequent with very intensive evaluation of a patient—frankly, much more thorough than the usual source of—of checkups that happen when someone’s on medication at physicians’ offices. Certainly in this context with people with mental illness, many of who go to drug monitoring clinics, drug therapy clinics where one physician is prescribing for a whole raft of—I’m not sure that, as a matter of empirical fact, there might not be protocols where you get more careful follow-up within a protocol than you do in center practices. The standard in practices is not very good, unfortunately, maybe particular to these people.

Finally, the fact that someone dies on a protocol does not necessarily mean that the study was unethical. A side effect of clozapine is that you get agranulocytosis. It’s a very—not always lethal, but it’s a very serious condition. It’s the price you pay for the therapeutic benefit. It’s a separate question whether they didn’t monitor those people in trial closely enough so they missed the early warning signs and made a small leukopenia much more serious. That’s a real serious issue of the protocol design. I think we have to be very careful not to go backwards in the fact that someone suffered an adverse event in a clinical trial to say, there was a problem with the ethics of the research design. There may have been, but I think we need to see that case worked out. In fact, responsible investigators will certainly.... Data safety monitoring commissions spend a lot of their time on just those cases going back over those unfortunate cases and say, “Does this mean we shut the whole trial down, does it mean we should modify the protocol dramatically to add exclusionary conditions,” and so forth. So, you know, it’s always easy in retrospect. You go back and say, “We should have done it differently. But if we don’t do the research; we don’t now what we should be doing there.

And there are two kinds of monitoring. We’re interested in this report in the data safety monitoring board, as a whole, but also the individual subject monitoring, and we’ll come back to that in some later discussion. Okay. Let’s turn to a set of recommendations that fall under 12 and the revision that appears on the memorandum from September the 15th on page 3. I noted already, but let me just—at the point in the text on 152 there is an addition about dissent from page 2 of the September the 15th memorandum. Just note that. Eric. Jack’s is not here. Do you want to say anything about Recommendation 12 as revised?

DR. MESLIN: That suggestion was simply that first and foremost the original Recommendation 13, which appears on page 153, is inconsistent with Recommendation 12A to D, and the easiest way of resolving that—it was an oversight in drafting and we apologize—is to simply divide up what is now Recommendation 12A and call it Recommendation 12. And the following three parts—B, C, and D—of what is now Recommendation 12—make that Recommendation 13, with the altered language that you see in the memo. And for those who may not—does the audience have the memo? Okay, then I won’t go ahead and read it. The proposal is to make this more clear and then you would simply delete what is in the text as Recommendation 13, focusing on

competent persons, and Recommendation 12 on those who currently lack capacity in the revised or proposed Recommendation 13.

DR. LO: Again, I have a couple of questions: In 13A a person is given consent for participation in specified future research. My question's whether the specification is to a specific protocol to a sort of class or type of study. I would favor the second—and in B, we're talking about patient—when competent, appointing someone as a surrogate specifically for research decisions. Does that appointment also have to specify the types of studies, or can I just appoint someone whom I trust and say, I'll rely on that person when the study comes along that I'm eligible for to make the decision based on what they think is best given all they know about me. What if I have to have said I want to be included in certain types of protocols? The danger I see there is that I can't anticipate what kind of research people are going to be doing in the future and I have to have said I'll participate in that type of research, let alone the specific protocol.

DR. CHILDRESS: Does D go—it goes a little bit farther in dealing with the kind of case I think you have in mind, but it may still be too restrictive.

DR. MESLIN: I was going to say in answer to your question, Bernie, the intention in making the proposal in the way that it was in the—to you use your language, the former—it was not specific, not specifically designated protocols but to specify type or class. The word “class” is not there. That was the intention, but it's obviously up to the Commission to discuss that.

Professor Charo: Okay. First I've got to say that it gave me a headache to try to read this. We need to simplify this. I'd like to not only add the two-comma rule; the two-semicolon rule. If you need more than two semicolons you make a list. Several things. First, we've gone around in part as a result of public comments a little bit about the nature of the prior set should be permitted, and much of what's going on here in between the various commas and clauses is an attempt to specify how precisely somebody has to have anticipated the specific research protocols for which they might—in which they might be enrolled by a third party. I would like, once again, to simply put on the table a simpler alternative, which is that people indeed are allowed, if they want to, to go by this kind of layered approach we've been using in the tissue sample area. Some people may want to say, “I'm designating this person to enroll me in research related to my condition” period. Have at least one simple option. This is only going to be used—I mean, again, I don't want to spend too much time on it, but it's only been used by about 11 people in the entire United States. But of those 11, at least 7 are going to wind up finding that the document is useless, that they weren't able to write it correctly. But if they were able to simply say, “I want my mother to be able to do whatever she has to do that she thinks is right for me.” I want people to be able to do that. I want people to be able to act they way actually act in real life.

MR. HOLTZMAN: This recommendation is the one which really brings home all of the real key issues—in many respects, that the hardest issue to grapple with—and I feel that we’re trying to finesse something here and it’s not working. I can very forcefully make the arguments why you should never do more than—do potential harm to someone if they can’t consent, and no one should be in a position to let them do that. I can make the arguments why we all know that it would be nice to have research which actually would help this class of people. To put in place a mechanism where I think the consensus is there will be next to no one who went up beforehand and provided a directive to someone that said, “Make sure I can get into any research including more than minimal risk or even just any research.”

Once upon a time I was a professional engaged in counting angels on pinheads; I don’t do that anymore. Okay? So, I real—and then—and I’m not sure I understand the language because we introduced language then about substantial harm—which when I thought we were in a minimal—so we ratcheted on down, and now we say, “But now we’re not uncomfortable.” So why don’t we call a spade a spade here. We should either say that research is off the table, okay? Just can’t be consented because—Alta’s explained it very well—pragmatically people don’t do these advance directives. And No. 2, most of us—most people can see how if we were to be interested in therapeutic research as opposed to nontherapeutic research, and therefore the legally authorized rep could be representing you. Or, we say—and that would be the cleanest way to do it, and then grapple with, if we’re uncomfortable with it, this—the continuum of risk. That’s why I keep focusing on the continuum risk, because I don’t want to screw around with consent process.

DR. CHILDRESS: Okay. Alta and then we’ll take a quick straw poll on this and see what is most interesting point.

Professor Charo: First I’ve got to tell you from the very beginning I was unhappy with the idea that even in minimal risk nontherapeutic research, you could be enrolled and was, you know, shot down on that. But I think it’s possible to say that people—it would be very easy to say that there’s presumption of people do not want to enrolled in nontherapeutic risky research.

And if somebody can come forward with whatever kinds of proof that’s appropriate to that IRB, which shows that in this case we’ve got somebody. And someone may come in with a durable power of attorney and others may come in with a tape recording, and if we can communicate to the IRB that they are to construe as narrowly as possible. We will have given the leeway we want to the few people that really have contemplated these things. We will have—make sure that it’s stringent, but we will not have to grapple with the details of what goes in, what goes out. Is it “written”; does it have to be witnessed? Did it have to be independent? I mean, it’s all going to be very situation-specific, and it would permit if somebody who very clearly has said, “So and so’s going to make all the decisions for me.” The only thing we’d insist

there is that they made clear that it was decisions in a research context as opposed to clinical. That's all.

DR. CHILDRESS: Okay. I think we then have three options floating around. One is the direction we have here, and I haven't heard a groundswell of support for this. And then we have directions like you were proposing, Steve, which wouldn't go as far, I take it, as you put in the kind of presumption that Alta would—although you might.

MR. HOLTZMAN: No. Actually it's completely consistent. Because I believe it is the case, the presumption is most people don't want to get involved in research that's potentially harmful and is not beneficial for the good of science in the world. Most of us don't think that way. I believe the pure place to fight the fight on this one is over what is the class of research, how much risk? Let's not confound it with consent issues.

DR. CHILDRESS: Are we in favor, then, of merging yours into Alta's? Alta and Steve will say it for us.

Professor Charo: As a substitute for what now constitutes Recommendations 12 and 13—Recommendation 13 on the handout. Thank you. We would say that nobody can be enrolled in greater-than-minimal research that offers no prospect of direct benefit unless the investigator who proposes to enroll them can persuade an IRB that there is—I don't know what word we want to use but—that they overcome the presumption that nobody wants this through some evidence of prior wishes. Some expression of prior wishes either to be enrolled in research of this type or to allow a particular third party to make decisions concerning enrollment in research in general; furthermore, that the IRBs should be extremely cautious on this topic when reviewing those kinds of special pleadings. Something in that vein.

DR. CHILDRESS: Without worrying about, now, exact wording and the kind of justification we might offer, how many would be comfortable with that direction? How many would like for us to go that way?

DR. SHAPIRO: I could certainly understand just eliminating enrolling these people altogether. That's very clear, and I think I could even support that because it's—especially if all the claims being made around here—that there are 11 people. You know, it doesn't become sort of moot in most ways and doesn't, certainly, impact scientific research in any way if there are 11 people who are going to qualify. So that I can understand that. I'm having a little harder time understanding how we're going to phrase in an effective way the capacity for the IRB to enroll nevertheless on the basis of some set of evidence, however described, that this person really wanted this. But, you know, perhaps it *can* be drafted in a way that would be helpful.

DR. LO: I want to say something that I think is going against the tide I'm hearing. I like Alta's formulation very much. But then I really have concerns, reservations about making the cutoff minimal risk versus nonminimal risk.

Professor Charo: Well, I'm not going to argue with you because I've always thought that enrolling people in nontherapeutic research without their consent or third party—they've asked to do it.

DR. LO: No. I'm actually going the other way. I think there's some research that's not minimal risk but not a whole lot much more than minimal risk which.... I think that's the point Steve was raising, isn't it? That's the locus of concern. We can either address it with the level of risk that kicks in these recommendations or the nature of the recommendations. I also would prefer to address it directly on the type of risk we're willing to allow surrogates to enroll patients who lack decisionmaking capacity into. Rather than trying to say we're calling it minimal, but it's really more than minimal.

DR. SHAPIRO: One, I don't think it's helpful to go back and talk about the spectrums of risk. I have—I think I have a very strong argument that that's a very bad idea at this time. Eric an excellent essay on that. I think in the end we really are fooling ourselves; we're not helping ourselves is the point, but I'm not going to go over that now.

I think there are two ways to handle risk: One is to say you can have two, three, four, eight, ten categories—whatever number you pick—and start trying to titrate that out; or, you can write things which are normalized on a level of risk. If you're trying to describe protocols, you don't try to describe them as whether they're images or not images—imaging protocols—but they are protocols which have a risk classification. And then you could try to normalize on that.

The Commission will have to decide, but I think that—I'm very, very worried about the categories they use in children's research and the capacity to deal with that. I think, in fact, we think we're dealing with something which is not being dealt with. You look at it carefully and you try to think of what the indexing policy requirements are for deciding between categories. It's virtually an unsolvable problem, and so I think that's a very bad direction to go in.

DR. GREIDER: I just would ask for some help—for somebody to tell me exactly what kind of research we're talking about that would be no possibility of therapeutic benefit, greater-than-minimal-risk. I don't have a clear idea in my head about it.

DR. LO: A patient with schizophrenia, depression, bipolar disorder in whom the research question is whether it's possible to correlate certain imaging patterns or PET scans or MRI scans or whatever later technology follows with either clinical prognosis or response to medications or levels of hormones, receptors, or something drawn in a bloodstream test. The bloodstream test—I take that the venipuncture is minimal risk, yes, except if the patient freaks out. But we've said that—my understanding of the prior discussion is we don't think MRI scans and PET scans are minimal risk for this population because they may well get anxious, agitated with those procedures. I just have to say that's true, but remember we're letting people say, “No, I don't want to do it

even though you don't think I'm competent." If they don't say that and the surrogate enrolls them and they go down to the PET scanner and they start to balk, it's standard procedure at any scanner if a patient shows agitation you don't just push them into the—whether they're competent or not. You stop the procedure and you deal with that. So, I think the actual level of risk that people are going to be subjected to—we're saying it's not minimal, but I just don't think this really is the same thing as giving someone a drug that's going to wipe out their bone marrow. To collapse that all together is not very realistic.

DR. CHILDRESS: Carol and Steve respond, then Harold who has to leave would like to offer some comments.

DR. GREIDER: This gets back to my earlier comment about what it means to do research, and what Bernie just described to me I would not put in the category of no possibility of benefit. Because, that is a research protocol that's designed to study the disease in the individual, which could—twelve months later, lead to the possibility of benefit for that patient. One person tell me why this is not beneficial to the....

Professor Charo: This person in the course of this study is not necessarily going to get any benefit. So that entirely changes the view in—my view of this, because I was thinking of, you know, an incapacitated patient in which you implant a tumor to see if it will grow. So, this not in my mind completely divorced from the treatment of the individual, because it's a research related to the disease, and if we could capture the language of "related to the disease."

MR. HOLTZMAN: This is somewhat in response to Harold. I want to keep the issue of consent pure and I want to acknowledge that in reality risk is on a continuum. There's just no way around that fact. But now when you start to direct the—see, I don't think three categories is necessarily better than two categories, right? But the problem you're now facing is if you say X cannot be done in the following situation, the category, that's where you've run into the problem, because you swept in maybe more than you intended, right? And this desire for another category is to try to loosen that up a bit.

If you—you could take the position well, I'm willing to live with that—I'm willing to live with none of those PET scans; some of us find that unacceptable—we're trying to find room for the PET scan but not the tumor implantation, and yet we're not being given the latitude for it. Now, one of the ways it may play out in reality if we write it this way is that people will start to broaden the concept if what is minimal risk. And I think that's anathema to what we're actually trying to accomplish, which is we're saying we want heightened scrutiny here; we want people to be sensitive to the fact that certain protocols might be more risky in this population. But if you write it in such a way that we're writing it, I'm afraid a practical result is, again, you'll get more winks and nods.

DR. SHAPIRO: Well, haven't got time today, unfortunately, to think about that full issue. I actually favor a situation where sort of something equivalent to Common

Law begins sharpening our understanding of minimal risk and it will float up and down and change as we understand it. I think, in fact, that you erect an extremely good argument. That's a far preferable way to deal with it than an arbitrary number of classes and we can't settle that today. I understand your point and I accept your point in part also.

Let me just say—I apologize, I have to leave but I do have to make a plane and I just apologize for it.

I just want to say a few words—not about this particular recommendation and so on, which Jim and others will go through and the Commission will decide how it would like to proceed. We will, of course, on the basis of all that's decided today, produce a new draft. We absolutely require your attention to that material as soon as it's ready, and your thoughtful responses to it, because we do have to move along here, do our best to get a report that is, in our view, a positive contribution to this area, and those of you who feel that somehow there's an important issue that we were—either didn't handle properly or you want to add something to it, of course there'll be room in the final report to express that. But Jim has said that once; I think I've said it once before. But—so, I think we all understand that. But the critical thing now is going to be feedback—thoughtful feedback, and we may schedule—in fact, the meeting, as Eric said before, a conference call meeting, so that we can meet together without having to assemble together, because it's very hard to get people from all over the country to an extra meeting. But that looks to me like more and more a likely possibility as we get down to these final stages. So, we'll probably—I don't know, Eric, what your feeling is, but it'll probably be something like three weeks to get a new draft, so that's going to put us in the middle of October. We'll probably try to give Commissioners ten days, two weeks to respond back. We'll have to have a conference call sometime. We'll generate—and then we're going to have to generate a final report and then allow some short period for any Commissioners who wish to add their own particular statement regarding any particular aspect of it. Obviously, the report is not going to be what any single one of us would have written if we had our way on everything. And we all have the areas where we would have gone somewhere else. But I think, and I believe on the basis of the discussion today, that we can get enough in agreement so we will have broad-scale agreement on most of the important issues—but perhaps not all. And, it's my own view that absolute consensus is not necessarily a great thing; in fact, it hides information in some cases. Other people made that point many times.

So, Jim, I apologize once again and look forward to the next draft.

DR. LO: Harold, you've given us a lot of good thoughts and very penetrating questions. Could I ask you to tell us how you would stand on the example I gave of the PET scan? Would you allow a surrogate to consent to that in the absence of some indication from a patient?

DR. SHAPIRO: I'd have some concerns about that in a nontherapeutic case. This is not advanced planning. This is an actual procedure. But I'm always open to good arguments.

Professor Charo: You know, Bernie, one of the things that may happen as a result of this is that people will begin looking for ways to make that generally minimal risk. I mean, as somebody who needed to be medicated before I could undergo my MRI because I'm claustrophobic, I was impressed that there were all sorts of things that people can do to minimize the problems, ranging from medication to massage to changing to the environment of the room to having a friend. There are all sorts of things that—where you have to figure it out. One of the classic things that happens in the law—in legal systems—is that you try to figure out where the pressure points are that will change behavior and move the system in the direction you want. It's possible that this will help to take those things that are in the—what you would call minor increment, and make people creative in figuring out how to make genuinely minimal risk so that people can be enrolled without opening the door to things that are far riskier than what you're describing.

DR. LO: If we say, great idea, Alta. In the protocol there's this provision that if the patient gets agitated they are offered the option between stopping the study or being medicated. Is that now minimal risk?

Professor Charo: No. I'm not saying dissent makes it minimal.

DR. LO: No, that's what I mean, that—well, are you going to routinely pre-medicate people who may not need it?

Professor Charo: I think you might routinely—you might change the way in which this is done. It doesn't have to be medication. You may be able to assess people individually—my thing is simply you might be generating an initiative toward creatively trying to make this less potentially upsetting.

DR. CHILDRESS: Diane wants to get in on this, and I have also Bernie and Trish and Eric.

DR. SCOTT-JONES: I'd like to emphasize what Alta just said, because I think we have to keep in mind that science changes constantly, and as Alta has just said, there will be different ways to conduct studies. Science moves in order to be more ethical if you demand it, so I don't think we have to assume that there will be no change in how science is conducted.

DR. CHILDRESS: Bernie, did you want to get in on this?

DR. LO: I absolutely agree that we should minimize risk and we should use creative ideas to avoid putting people at unnecessary risk and identifying people who are more likely to have an adverse effect and anticipate. But I think at some level I'd like us

to acknowledge that some research is going to be more than minimal risk under the definitions we've been working with. Even after we've done everything that Alta noticed and suggests. And I'm saying that if that's the cutoff for basically not allowing it, you're precluding a lot of useful research on conditions that are going to lead to the therapeutic benefits that you're hoping for. And it's like what Eric pointed out yesterday, that's the classic dilemma in doing research. It's the long-term benefit to society as a whole versus the harms that people undertake in order to achieve that goal. And it's that tension and where you put the fulcrum. At some point we're going to lose some research no matter how hard we try to reduce the risk.

DR. CHILDRESS: Okay. Eric, Trish, and then Laurie.

DR. CASSELL: Boy, you talk about back and forth and back and forth—I was for it, I'm against it, I'm for it, I'm against it. I'm now convinced in fact that the problem is serious enough so a solution—we have to try and find a solution to it. It might be that we add—this is a point in which we add the responsible health care professional to monitor the procedures. And, so that there's somebody protecting that person.

Professor Charo: I—you're going to add that, but the person can't be enrolled now at all.

DR. CASSELL: We enroll them knowing that there will be a responsible health care professional not part of the study.

Professor Charo: For all levels of risk? Only minor increase, something....

DR. CASSELL: No, I'm allowing—no, I don't think you can do that. I don't think you can specify—unless we—I mean I know that one of these days this Commission is going to decide we have to solve the risk problem. At the moment we haven't, and consequently I'm trying to add in there some third party who is not part of the program, who is there, and you can't minor above, little above—it doesn't work. But you do have an IRB to understand that this is our problem. It's a problematic area where maximum protection of the subject has to be exerted because of its problematic nature, and then the IRB acts in that regard.

DR. CHILDRESS: I have Trish and Laurie, and then I know that some people have to leave around three. So I'm going to push this and try to get a sense of direction here that is what we think—what the majority of the group would like to do—and then we'll see if we can talk about a few other recommendations before we close.

MS. BACKLAR: I'm sorry—I'm going to go back to something we really don't want to discuss, and Carol brought this up so I can blame her. This issue of benefit and therapeutic research. And I'm not sure if I'm pronouncing Robert Levine's name right. I do wish in a sense we would invite him back because he certainly comes from this perspective that to use the word “beneficial,” “of benefit,” or “direct benefit” is a very peculiar word to use in research. And I would like to say there are clear research

protocols which are minimal risk and under that, and then there are protocols which go on a kind of continuum—which one needs to explore, perhaps in a kind of casualistic fashion, of where you go from minimal risk up this way. And I think we have confused ourselves. This is a perfect example—of Bernie bringing up what you’re going to do if you’re going to put somebody in an MRI, which is very useful, or a PET scan or all of these things which we all agree is not really going to harm the person. It may frighten them and then we let them out. We don’t force them to do it and so on and so forth. But it’s certainly not something like a challenge study of the kind that we have been reading. And so we certainly don’t want to close the door on that. Therefore, I think we may have to seriously think through of making the categories we put here about benefit and try to describe the risk on some kind of a continuum. I don’t know how to do it. That’s all.

DR. CHILDRESS: Laurie....

MS. FLYNN: Well, I think I just would follow on to what Eric and Trish said. It’s completely unacceptable to cut off this much research, given the suffering that these folks endure, given the low level of therapeutic benefit that’s still available to them, given the basic sciences is where we have to be in terms of understanding the functioning and the mechanisms of the human brain. It’s just unacceptable to arbitrarily cut off all access without any other kind of ability to, as risk increases, to then increase protection. We would, as I think we heard earlier, not even be able to really compare what’s going on in the brains of individuals with bipolar disorder versus individuals with schizophrenia when there’s considerable suspicion now that in fact these may not be two separate orders but disorders on a continuum. There’s a lot of significant basic understandings of what’s going on in the human brain that I think we would simply say could not be done. And I find that unacceptable and I would recommend we think through some way to more carefully match risk with protection than what this does for us.

Professor Charo: I appreciate your frustration. And indeed I was expressing similar frustration on the last go-around on research that offers the prospect of direct benefit. But I also think it’s possible that we can overstate the research that’s going to get lost as well. So, if we’re going to be talking about what’s really at stake and are we willing to live with our decisions, I think it’s important to be even more precise. The research with PET scans and MRIs can all be done with people who are competent, even if only fluctuating, because either they can consent at the moment’s going to be done or those are the very people who can be approached and asked during your next episode, “Would it be okay if we did this to you?” Right? So that that is exactly where this kind of advanced planning is going to suddenly become the avenue people are using, or looking to use. Alright? And, as a result, I would welcome a description of those things that absolutely could not be done, a scale of those things, and the impossibility of reducing the risk that’s associated with these procedures to something that would genuinely match what is commonly understood—whatever that is—as minimal risk. So I

understood really what's at stake here if we were to live by this kind of simple two-party system.

DR. LO: I mean, I would like to get a request to someone at NIMH to answer Alta's point directly, because I think that would be important to give s a sense of what would be giving up if we actually made these recommendations.

DR. GREIDER: Well, at the risk of being really heretical here, one of the responses to the issue that I raised, which is really two issues, it gets to my fundamental understanding of the term "research," was the reason that there's a difference between therapeutic benefit and nontherapeutic benefit is because the regulations say that. The regulations say that if there's a direct therapeutic benefit to these people, it's different than if there's a long-term—how I would characterize a possible long-term benefit. I wouldn't draw the boxes that way at all, and I just want to point out that part of what we're going around about here is because we've decided to put this in the current context under the current regulations. And I'm not sure why we have to adhere to a framework that was laid down ahead of time rather than coming up with what we think is a useful framework.

DR. CHILDRESS: We're probably going to have enough problems making the changes we have to make.

DR. GREIDER: I realize I was raising all kinds of other problems.

DR. CHILDRESS: I challenge that. But any other general points to be made, because what I—it seems to me we have three options on the table and I'd like to get some sense of—one thing we certainly had a request for is to get more information about the sorts of things that would be lost. That could not be done. And so we will pursue that. We could get that probably within a week actually. With telephone calls and e-mail we can get at least some indication and give us some sense of the ballpark we're talking about.

But we have—the model that we have here on page 3 we talked about—the consent in various ways in advanced planning—we had Harold's no to this category of research, and we had the presumption model. Those are very brief and cryptically stated, or the three models it seems to me we have been talking about here. Is there anything missed, and is there something else—? One we have before us here, that was the first one. The second one is basically no, we don't do greater-than-minimal risk research. It doesn't offer the prospect of direct medical benefit unless we have direct immediate consent. Forget this advanced consent stuff. And then the third would be to work with the presumption against doing it, but then to allow it to be done when you could have evidence about the person's prior wishes—that sort of thing.

DR. LO: I would like the recommendation to allow nontherapeutic research under the current understanding, taking into account Carol's reservation. That's slightly

more than minimal risk. It should be done with the approval of a legally appointed surrogate subject to the kinds of protections which would include Eric's suggestion that an independent physician monitor the patient in the course of the trial as the patient's representative, and Alta's previous suggestion that really rigorous, creative thought be taken to making sure that the risk really has been minimized.

Professor Charo: Bernie, from what I understand, the only two kinds of studies that have been mentioned to date that fall into what people are calling minor incremental minimal risk are MRI and PET scan. I've never heard a single other example of a study that people want to do that would fall into this mystery third category, right? So far. So what's the advantage of creating—you are creating a third category. You're creating an intermediate category with an intermediate set of protections that allows the research to go forward, more than—more protections than if it were offering the prospect of the direct benefit as commonly understood, but fewer prohibitions than if it were nontherapeutic entirely. What's the benefit of creating a third category as opposed to issuing a list? Special dispensation. Which goes, you know, type of research by type of research or people can debate it over exactly what this research would offer and exactly how comfortable we are about drafting people without their consent into this research for the purpose of providing a benefit to society at large. We're going to draft them just like we draft soldiers. Because they're the only people who can do it for us. Only the people that have this disease can serve this societal purpose, so we're going to draft them the way we draft soldiers. And let them debate it protocol by protocol for a special list.

DR. LO: My main concern is that we not effectively close all research like that. I don't know enough about the fields to know what other types of studies are in that category, and that's why I supported your suggestion to get more information on that. I'm not wedded to creating a third category, but I just want to find some way to make it reasonable for investigators to get that kind of study approved providing it's done all the right things. I certainly think stimulating debate directly on that point, discussing, and so forth is really valuable, and, you know, we've talked about the views and the Common Law of understanding, things like that. I would support that. But my major concern right now is that we not totally preclude this kind of research in our regulation, in our recommendations—or force people to blatantly misinterpret the plain meaning of the words in the regulations by saying, "It really is minimal," when in fact, you know, it really wasn't.

DR. CHILDRESS: We're going to request additional information, but let me just see if anyone in the audience in two sentences, three sentences could give an example of something beyond what we've talked about that might be ruled out. Anyone? And if you'll identify yourself for the record.

DR. SHORE: David Shore, National Institute of Mental Health. Certainly research involving spinal taps, looking at cerebrospinal fluid metabolites of neural

transmitters, which may reflect treatment effects or predict treatment response for the next group of patients might be certainly within this category. We talked the last time about genetics studies in which you're dealing with an affected sib pair, and if in the case of Alzheimer's disease, by the time the younger sib develops the disorder, the older sib is almost invariably not competent to consent, and since this involves genetic research this group has tended to see that it is greater than minimal risk. Arguably the most dramatic medical progress in neuropsychiatry has been the discovery of four or five genes which directly increase vulnerability to Alzheimer's disease in specific individuals. If you were not to allow research involving the elder sib with severe dementia, we simply could not have found those genes. We simply could not be developing mouse models. We simply could not be determining which drugs or interventions might prevent the development of that illness. We could not predict which patients with other types of mood disorders or schizophrenia would respond to treatment. There are numerous answers to that question. However, based on—I mean, the fact that you have a letter from Mr. Aller and the fact that Freedom of Information requests have been used in the past to tar some of our investigators, I would like to find a way to provide information to NBAC in such a way that investigators who have conducted such studies would not find themselves the victim of media assassination or lawsuits.

DR. CHILDRESS: I think the information we're requesting need not be tied with specific studies but rather can be generic in nature, and what you've just provided is helpful but it would be helpful for you and your colleagues to provide fairly concrete examples that may not be specific to particular protocols. Eric. Thank you. Eric.

DR. CASSELL: Where we are now is there is a general feeling that there are kinds of research that must go on but that do represent some risk but of no benefit to the individual subject. We are worried that giving advanced directives of any kind and the surrogate might put somebody at really great risk. We're worried that that could happen, but we're not so much worried about this PET scan with cautions and so forth. So, I don't see why we cannot specify the protections that we've already talked about, including the neutral observer—neutral medical observer—and provide a set of examples that might be acceptable if the IRB—remember, this is—we're not speci—say yes or no in IRB. It might be acceptable to the IRB if they understand what the problem is. And so we're trying to keep from free rein. You can do anything you want. That's the thing we're trying to stop. We don't "anything you want." So, with examples, but not with people because the day after tomorrow there'll be a new procedure, and if we could do that, I don't, myself, find that objectionable. I can accept that.

Professor Charo: I'd like to take the examples that were given and kind of work through them. Why not, right?

DR. SHORE: This is only a partial list.

Professor Charo: It's only a partial list, I understand. One has to do with genetic studies, and the example of why this would be undoable was premised on the assumption that it would be found to be nonminimal risk. If it were found to be minimal risk, it's no obstacle. And on the assumption that it was not possible, or at least not easy to get prior planned consent—because that also would make it possible, right?

DR. SHORE: Well, again, based on your discussion from this morning as compared to yesterday afternoon, if you're going to say that every subject who's competency must be questionable needs to provide informed consent, and the consent cannot be waived, then you have in fact made the issue of minimal risk irrelevant and you're treating all research as greater than minimal risk.

Professor Charo: Actually, no. First, we've never said that you can't waive in these circumstances under the same criteria in which you can waive consent generally. But more importantly, if it's minimal risk, then according to the recommendations we've been debating so far, a third party could volunteer this person as a subject without any real complication.

DR. SHORE: Well, as Mr. Holtzman noticed in a previous meeting of this very Commission, that many IRBs, because of the kinds of risks to ensure ability, confidentiality, etc., routinely considered genetic studies to exceed greater-than-minimal-risk. So I think until this issue is resolved, I think there is a strong possibility that local IRBs are going to judge research on the genetic basis of these disorders to exceed minimal risk, and therefore the older sibling who will be unable to consent—and the research will certainly not benefit that older sibling—it might benefit his or her children, but that's irrelevant for this purpose.

Professor Charo: Right. So, actually we could generalize it to pedigree studies in which somebody—I'm sorry.

DR. CHILDRESS: Three people are going to have to leave by three or shortly thereafter. So what I'd like to is actually for us to carry on this with some written examples and try to elaborate that. And what we need to do if we can is get some sense of where you'd most like to go of these five options. Do we consider Eric's list as a modification of Bernie's, or as a fifth option rather than just sort of list exceptions. Rather than simply say, "We're going the direction of slightly more than minimal use," carve out very specific exceptions. But if we could get—and we may not be able to do it, and that's understandable if you can't, but it would be helpful if we could—of these possibilities, what we have here, and I've heard a lot of reservations about that—Harold's view of saying no to this kind of research, if it's great than minimal risk, nontherapeutic, no potential, no prospect of potential—direct medical benefit—and presumption against the research but aligned for the possibility that there might be some, perhaps even given these examples, more than eleven, who would go through the next planning process and authorize either a proxy or some other way of participating in the

research. Bernie's proposal of nontherapeutic, slightly more than minimal risk, and then Eric's list approach. Let me just run through it and see, quickly, where your sympathies are.

DR. GREIDER: Can we combine four and five?

DR. CHILDRESS: They are different. I think it's—if you open the door, I think that the—we can combine them, that'd be fine but I think it's one thing to carve out some very, very specific exceptions. Another thing to say—.

DR. SCOTT-JONES: Then we have to have two rounds of voting.

MS. BACKLAR: I thought you said that what we have here is five has become three. Correct? Dissent has become the third one.

DR. CHILDRESS: Let me let you go through it one by one. How many are in favor of going the direction we have on page 3 for the revised recommendation 13, which is the—well, as in the document of 9/15? Okay. How many would go Eric's—Harold's direction of saying no to a nontherapeutic research greater than minimal risk? How many of you would be in favor of what I—our version of what Alta suggested in earlier point, a presumption—

it's a recommendation what to do with nontherapeutic research greater than minimal risk. How many would be in favor of a nontherapeutic research greater than minimal risk? How many would be in favor of a presumption against that, but recognizing the possibility that some might engage in advance planning so rather than saying no, rather than basing everything on a model of a consent in advance through either specifying the research or designated proxy, when we just work with the presumption but allow the door open. Now, the problem with this one is it doesn't really open to the risk side and that's what some are wanting to do. On the next one or two—

Professor Charo: So they're not mutually exclusive.

MR. HOLTZMANN: Can I ask for clarification from Alta when she thinks about that one? Suppose we've got one of those eleven people who said, "It's fine with me to do nontherapeutic research that's more than minimal risk. So, you've got that advanced planning. Now we're looking at a protocol that is absolutely dangerous. Is it okay? Or, is what you have in mind—.

Professor Charo: No. If the IRB has passed on its reasonableness of risk versus—you know, risk in relation to the size of the question? And if the person's statement really clearly seems to accomplish this, sure. I mean, I'd be glad to hear what they had said. That's the whole point of having a case-by-case review of what somebody's said or done.

DR. CHILDRESS: And as someone noted, these—one could vote for three and also vote for A or B. Any in favor in this direction?

Professor Charo: So they don't want either the current or the revision. They don't want anything. So we're voting on No. 3 now.

DR. CHILDRESS: We're moving ahead now. So let's keep going. Have you voted yes? Okay. How many would vote for the presumption against, recognizing the kind of research, but opening the door for the advanced planning for the few who did it?

DR. MURRAY: Wait a minute—opening the door for what?

DR. CHILDRESS: For the advanced planning. What we're doing is getting a direction of where people want to go with the revision. We don't have the formulated options here other than what we have in the text.

Okay, a little support for that. We have nontherapeutic research with slightly more than minimal risk—Bernie's proposal. How many are in favor of going in that direction.

Professor Charo: What are you going to do, create a list?

DR. MURRAY: Does this—wait, is this the list or does this acknowledge that we will—we are creating the third category as slightly more than minimal.

DR. CHILDRESS: How many are in favor of going in that direction. Okay. How many in favor of—we'll call it 4B since they're similar in many ways, but how many would be in favor of Eric's direction with a specified list of exceptions but without the kind of flexibility?

MR. HOLTZMANN: Wait, I need clarification. I also heard you say, I believe—of course we won't have a complete list, so—but if it—did you envisage that the list would be—these would be the exceptions: A, B, C, D. Or did it say “and others of this type”?

DR. CHILDRESS: Yes. So therefore it is no different.

DR. CASSELL: It's different because it specifies for this purpose only. We don't say “We now have a new category called greater than minimal risk.” We specify “such as.” Now, that's a common thing in—.

MR. HOLTZMAN: But, okay, now, but what's the organizing principle by which you're going to put things on that list and also say “and others like them in the future that are similar”?

DR. CASSELL: Wait a minute. What makes it different? Because it does not give official credence to a third category. It specifies for this purpose and this purpose only interventions “such as.”

DR. CHILDRESS: Or, put differently and perhaps less charitably, “it smuggles the third integer”—.

DR. CASSELL: But it does have—but you see, if you start putting that in, then we’re back into that whole risk thing, everything.

DR. MURRAY: Let me suggest a different analogy. The IRB—the whole—the Federal rule requires that there must be a whole IRB review except when it falls one of the categories for exception. I think you’re looking for us to build something analogous of the category of research which is exempt from the whole issue, or research which is eligible for expedited review. That list, research A, B, C, D.

DR. CASSELL: There’s another part to my proposal, and that is with the added protection.

DR. CHILDRESS: But that would be included.

MR. HOLTZMAN: I’m genuinely confused, okay? I understand what it means to specify something. I also understand what it means to give the extension of a concept through substantiations. But if you’re allowing that there can be more, you’ll have to specify the intention of the concept to provide guidance for what else will go onto the list.

DR. MURRAY: Steve’s right. You can’t say “and stuff like this.”

DR. CHILDRESS: Okay. Alta, and then those people having to leave. I want to run that proposed—is that—Bernie, we will look forward to hearing from you with a concrete proposal on this. Eric, the same from you, and quickly in the next few days. Write out something. Give us direction here, and let’s—because we can’t resolve it today and we do need some—and we’ll also be getting further information about the kinds of things that will be lost if we went one of the other directions. Okay?

Since people are having to leave, what else do we need to talk about in the recommendations? Where else do you want to focus in the few minutes we have before we lose our quorum, whatever that is? Other problem areas? Still have no problems with our notification discussion? We had suggested—this is No. 4—we had suggestions about *how* notification would occur—or *could* occur—and it’s important, I think, to build that into the discussion, which hasn’t happened yet. But I think it was general agreement that that was important. But anything else about notification?

Professor Charo: Oh, no. No. I’m sorry. I was on to the legal authorized representative option.

DR. CHILDRESS: Okay. Let me just see if there’s anything about dissent—you know, the change that’s been made there. I’m looking away from no apparent dissent. Okay? I guess one proposal I would make, if you’re with me on 145 for a moment, I think it makes no sense to have Recommendation 6 as a separate recommendation. It’s really a qualification of 5 and I would strongly propose that we just include that as the last sentence of 5.

Anything else you want to focus on? Let's look at the legally authorized representative issue.

Professor Charo: It's the end of the memo that was handed out with a long separate memo from Jack Swartz. You know, I think in the context of responding to the comments, there was some draft text that we distributed on e-mail that would have limited the legally authorized representative to family members. I know I must—I was one. I don't know if there were others who wrote back and said that they seem to deliberately exclude friends and that this may not be appropriate. It's a special concern to people who are homosexual because they're not allowed to marry in the United States. It's a concern generally for people that really are very close to their friends and not with their families. And then it showed up again as a possible recommendation of how States can change their laws about what constitutes a legally authorized representative, which I think was a pendulum swing that went way in the other direction. And there's a perfectly sensible recommendation—potential Recommendation 15 that says simply we should understand that legally authorized representative includes people who, under the law of the State where research is conducted, can serve as proxy decisionmakers. That means those states that had thought to put in "friends." Friends would not be excluded by our recommendations. Those States that have not thought to include friends will struggle along with that issue in the clinical context where it's more frequently raised.

DR. MESLIN: So you like the memo's version of Recommendation 15.

Professor Charo: Yes.

DR. CHILDRESS: Okay. That's page 4 of the 9/15 memo.

MR. HOLTZMAN: I agree with that, Alta. I have a question to you since you raised it in the e-mail. States will do what they want to do. It's part of the purview of this Commission to note that there are States where those statutes would not include the potential for friends and it's therefore worth their thinking about changing some of the contents?

Professor Charo: I think it's perfectly—I think it's worth our while to note that the exclusion of friends has problems, and that it has special impact on certain sub-populations in the U.S. I think that making a recommendation that States change their laws on this point is probably more than we need to do. They'll do with it what they wish.

DR. CHILDRESS: Jack has joined us—and, Jack, feel free to add to any of this discussion. Bernie....

DR. LO: Before people break up, I can't find it now in the chapter but when I read it through before I was concerned about a recommendation, which now I can't find, that IRBs be responsible for monitoring untoward side effects or something?

DR. CHILDRESS: I hope that was eliminated.

DR. LO: But I think it would be reasonable for IRBs to require in cases that are a lot more than minimal risk, without creating a need for a third or fourth category, to make sure the protocol has in place—a system to monitor individuals in a study for adverse side effects—for example, through the appointment of a physician, whatever, dedicated to that person, who is different from the principal investigator of the study if that's—the patient's treating physician. So, I think—you know, I think the concept is good. I just don't think the IRBs should do it themselves. They should make sure the investigators put in the protocol a way to do it.

DR. CHILDRESS: And by the way, on all these points—I haven't talked to Eric, but I'm hopeful that we can get a transcript very, very quickly on—that meeting is today, so we can actually use that as we're thinking further about the revised draft.

Professor Charo: We're getting close to closing? I would like to propose an experiment to people as they leave here today. I'd like each person here to imagine when they get on their very planes to go home—and I apologize, Trish, for you—I want you to imagine that unbeknownst to you somebody volunteered you and the other people on your plane for a special experiment in how scary it is to have an emergency. And suddenly an announcement goes on telling everybody that the plane is at risk of crashing, that you should get your shoes off, get your glasses, that you grab your knees, you should get your life vest, read the thing, and it goes on for 10 minutes. And then at the end of that they say, “Actually, you know, this was just a test to see how people react because we need to understand how to make it possible for flight attendants to handle the panic in a plane. It's crucial, because in a plane you can't have panic that goes riot.” And it wasn't that you volunteered for it. Somebody volunteered you for it. As a thought experiment, you'll appreciate what's at issue in volunteering people for things that are not harmful—it's only going to frighten them—where it's not possible necessarily with a mere dissent to eliminate all of the frightening aspects of this experience. Just so that we can have some empathy with what's going on as we figure out if it's worth it to do this.

DR. MURRAY: And on the way my plane, upon landing, it suddenly geared up. The shuttle pilot came on two minutes later and explained there was another plane on the runway.

DR. CASSELL: The problem with that is that my colleague on the left just told me that a list is not like an analogy and since you gave a case example so that we could use it as a thought experiment, so I find that unpersuasive. But the much thing—much different than that is these are not people who are being volunteered out of the blue—healthy volunteers. They have no relationship to the thing that happened at all. Not only that, the person who volunteered these people had no knowledge of their mind, no knowledge of what's bothered them in the past, and so forth. This is a totally different situation. It's the difference between sickness and health.

DR. CHILDRESS: It looks like this is deteriorating rapidly, but before we close, are there any other recommendations you want to call our attention to and staff's attention to or you think we need to do further work? In general are you comfortable with the other recommendations? Going once, going twice—.

DR. CASSELL: With one caveat. There are differences in the way the thing is described in various places in the document. For example, the neutral health care professional. That makes them not the same each time and I think we have to be very careful about that.

DR. CHILDRESS: And if you have—thank you for that general point, but if there are very specific things, would you call it to our attention.

MS. BACKLAR: Well, like I'm sorry for harping on the same thing, and I'm grateful for Carol for bringing it up. I think that we are—I think we have been put into a box by the direct benefits, and that if we want to have minimal risk and greater-than-minimal-risk, we have to get ourselves out of this box and find some other way of describing researches against riskier and riskier and what we do and don't agree to. That's all. And I think that—I understand your point, we can't change everything. But we may find out that we have done very little good by staying in a box that has been given to us, which really is no longer making sense; which is again—I would like to have some advice from Robert Levine, who has thought about this a great deal and may in fact have some good suggestions for us.

Professor Charo: You know, it's possible that we're thinking about this problem the wrong way. The box isn't created by the regulations. We've created the box in the following fashion. Everybody recognizes the difference between direct and indirect benefit. What you were describing, Carol, is a long-term consequence of participating in these studies would classically be described as an indirect benefit. If the studies yield advances, this person may well be one of the many people who will benefit from those advances. They're not benefitting from this intervention so much as the long-term knowledge that's gained from it. It was earlier in the day that we said that we were limiting the notion of research that offers the prospect of benefit and therefore allows for easy volunteering to situations where it's direct benefit. It's not that the regulations put us in the box; it's that we chose to be very narrow, and so it is not a matter of changing the regs—it's up to us. If you want to say that the prospect of indirect benefit is enough to volunteer people, we can argue that out. But that is now opening up the door to like a gazillion things that may pan out in the distant future, so it's a slippery slope here, and my initial problem was that people were assuming in the research with possible direct benefit—people just slip in the mindset that that is going to benefit people, when in fact there's a high probability that none of those people will benefit at all. So if we think about the probabilities, even in that category that we're calling benefit, there's no guarantee that there's going to be any benefit at all there, and it's exactly the same thing

true for experimental studies—PET scans, whatever—on the same disease probably have overlapping probabilities about whether they're going to benefit that person or not.

DR. GREIDER: Well, no, because the second category is zero prospect.

Professor Charo: No, it's not. It's not.

DR. GREIDER: There's a probability that there will be some experiment done with venipuncture or a PET scan or whatever, and they'll find out. They can then turn around and treat those same patients that went into that research protocol. So I see it as a realm of probability of benefit out the patient if it's directly related to their illness. And one of those probabilities is in this box, and the other one overlaps in this box. And I see that it is completely arbitrary to break those into two different categories if it's directly studying the disease that the person has. So that's the box I think we've put ourselves in.

DR. CHILDRESS: Okay. You have at your desk—you received after lunch the statement Alex submitted to revise No. 3. Is there any comment on that before we break? Everyone should have it.

MS. FLYNN: I need to find it; I already put it away. But I think that it should still have some language that doesn't make it seem that capacity assessment is fairly straightforward, because it isn't. Capacity assessment may or may not actually reveal the person's capacity, so I think we need some language, and I had suggested this earlier, that would be something like, you know, the researcher would need to provide some justification for the method used or something like that because capacity assessment is not easy, and part of having decisionmaking capacity depends not only on your internal capacity but on how well the researcher explains research to you—I just find it problematic.

DR. CHILDRESS: Could you offer, of course, a revision; and second—even if we stick with this language, for instance, after further reflection and proposed revision, it would still be helpful for you to provide material for the text. That is, part of what you're suggesting, it seems to me, is something that would be very important for interpreting this, even if it is not incorporated into the recommendation itself. But if you could think about that and submit that to Eric. Getting down to the final comment or two—Bernie...?

MS. FLYNN: Okay.

DR. LO: Just a comment on Alex's amendment. Again, I still have my concerns about do we need this for all protocols or particularly for ones where the principal investigator has a dual role as also patient's primary physician. I was just wondering, would the approval of the patient's primary physician fit as appropriate assessment of capacity? The goal here is to avoid situations where the—Eric, you brought this up earlier—where the principal investigator is—it's going to be very hard for the patient to say no to the principal investigator for a whole lot of reasons. The doctor may be the

private physician providing ongoing care; the patient may be institutionalized involuntarily and really dependent in that sense. And in some of those situations I very strongly agree. We need some independent research team who's qualified to do it. But if you're in a situation—well, one of my patients was just admitted on a involuntary hold for relapse of his bipolar disorder. Now, he's not on a research protocol, but if he were to be on a research protocol, he and his wife would call me and say, "Do you think this is a good idea?" And If I said—if I was asked by the investigators, "Do you think he is competent to—has the capacity to consent at this time?" and I went and talked to, without learning MacArthur protocol—which I don't know—would that—but I know this guy over time. We've talked, not about this, but life in general. Would that be permitted? I mean, I think we're looking for protection, and I'm not sure there aren't other ways to get protection that aren't covered by....

MS. BACKLAR: It's interesting, of course, because in minimal risk research—psychosocial minimal risk research, often that is exactly what is done. It's before somebody is brought into a recent protocol. It is ascertained from their clinician whether or not this person could be approached even.

DR. LO: If he can be approached do you think he's capable of consent?

MS. BACKLAR: Right. And in fact the reason you're asking if he can be approached is because they're asking is this person going to be capable of consenting.

DR. LO: I'm talking about independent assessment so that someone's not sort of pushed into a study against their better judgment without necessarily having some independent qualified professional assess them.

DR. CHILDRESS: But again, this is a presumption that's a rebuttable one. That's the reason for going this way. Okay? It's only a presumption, and you've offered persuasive grounds for using a less formal means of assessing somebody's capacity. It seems to me that's what this allows. That may still go to far for you, but it's different from what we had before. It opens the door in a way the other one did not.

Diane....

DR. SCOTT-JONES: I think what Bernie said is related to the point that I was making, that we're not in a position to endorse a way of assessing capacity, that what Bernie said he would do might be as good as some of those methods that we've outlined in the text of assessing decisionmaking capacity.

DR. CHILDRESS: Well, we're not recommending that particular one. This says "only an appropriate method which the IRB has to make a judgment about." "Administered by a qualified professional who is independent of the research team."

DR. SCOTT-JONES: But I think when people read the report and they read that, they'll go back to the section where we go through the methods of assessing capacity and they'll figure that we believe....

DR. CHILDRESS: I think we're very clear there, as a matter of fact; and if not, we should be, so when you look back over it and you think we're not—and I don't expect everyone to have read this draft through and carefully and every word this time. I didn't. But this has changed a lot, and it's changed a lot in relation to the kinds of concerns that people have expressed. I think Eric did read through it all, probably word for word. I think the draft as a whole is a much better draft. I think we still have a lot of problems with the recommendation and in connecting, then, appropriate text with the recommendations and pulling out things from earlier in the text that were made that were very, very important. But I think the discussion in the text is much more—is much clearer and much more nuance actually than it was at an earlier point. However, one question was raised and I'd love to get a—Trish has forgotten she told me to remind her if she hasn't mentioned it, and that is a question as to whether it would be good actually to put the second chapter in an appendix. It's the history of regulatory efforts and it, in a way, does break the flow. One could add a few sentences about what it's done there up in the first chapter when we're setting a context for the work in the report, but Trish, do you want to say more?

MS. BACKLAR: Yes, I thought that perhaps that could go in the appendix because that really is background material and I think when people come into read this, they're going to really want to know what it is that we're asking them to think about and to do. And I think that then they might like to go back and see what that background material—how it has affected the way we have come to this. But I'm just concerned that it will still be off-putting right at the beginning in there, sort of trying to get information out. That's all. It wasn't that I didn't think that the chapter was useful; I actually thought it was very interesting and very useful.

DR. CHILDRESS: It's only about 15 pages long, so we could make an appropriate appendix with a few of the points drawn into the first chapter as appropriate. But any sense of that? In general, it could appropriately go into the appendix rather than into the text. And then you would have pretty nice flow from setting up the research in Chapter 1 to informed consent to assent/dissent, etc., to risk potential benefit, and our concluding chapter. I think it would make a neater report.

Any last comments?

MS. BACKLAR: I only want to say again I'm very concerned about putting people into research where they haven't made any choices at all, even about their legally authorized representatives.

DR. MESLIN: We have important writing assignments for those who have already indicated that they would prepare something. But all the rest of us, if there are

things that we want to work on and want to see in a different form, then we need to provide that material in writing. Let me thank all of you for your very hard work today. I think we reached the end of our productive labors. And let me see if Eric has any concluding words. Thank you all very much.

DR. CASSELL: Only to remind you that our intention is to turn a draft around within the next two to three weeks. We are scheduled to meet, again, on the 20th of October unless that, for any number of reasons which relate to fiscal year in the government, could change. But we are intending here in Washington, D.C., on the 20th. The reason we haven't given you the exact location is we've been prevented from doing that in a sense. But we'll work extremely hard on staff to turn a draft around. The way that we can do that is if Commissioners will give us their written comments that have written on their drafts. Either leave them with us or Federal Express your packages to us. It's much easier to have it quicker than to ask you for it later. And, as I say, we will attempt to get all of the information that you have asked us for and to make the transcripts available as quickly as they are available. And I would like to thank the public who came out the meeting and has been so attentive and so helpful, as well as those who gave public testimony today. Thank you very much.

DR. CHILDRESS: Second all that, and thank the staff very much for the continuing important labors. Thank you.

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