

**25th MEETING  
 NATIONAL BIOETHICS ADVISORY COMMISSION  
 November 17-18, 1998  
 The Crystal Ballroom  
 Mayfair House  
 3000 Florida Avenue  
 Coconut Grove/Miami, Florida**

DAY ONE - Tuesday, November 17, 1998

Welcome and Overview of Agenda  
 Harold T. Shapiro, Ph.D. . . . . . 2

Discussion and Approval of Final Draft, Research Involving Persons  
 with Mental Disorders that May Affect Decisionmaking Capacity,  
 James F. Childress, Ph.D. and Commissioners . . . . . 5

Discussion of President Clinton ' s Request Re: Embryonic Stem Cells  
 Harold T. Shapiro, Ph.D., and Commissioners . . . . . 80

Public Testimony . . . . . 109

DAY TWO - Wednesday, November 18, 1998

Opening Remarks  
 Harold T. Shapiro, Ph.D. . . . . . 1

Discussion of President Clinton ' s Request Re: Embryonic Stem Cells  
 Harold T. Shapiro, Ph.D., and Commissioners . . . . . 1

Discussion of Staff Draft, The Use of Human Biological Materials in  
 Research, Thomas H. Murray, Ph.D., Kathi Hanna, Ph.D., and  
 Commissioners . . . . . 3

Research Involving Persons with Mental Disorders That May Affect  
Decisionmaking Capacity ..... 33

President Clinton ' s Request Re: Embryonic Stem Cells ..... 46

The Use of Human Biological Materials in Research ..... 49

## WELCOME AND OVERVIEW OF AGENDA

DR. HAROLD T. SHAPIRO: Thank you all for coming here today. As you know, we have an extremely full agenda today, including the final drafting of our capacity report. In addition our agenda is, as you know, further and important discussion regarding human biological materials in research. However, there has been a particular development during this last week that occasioned a letter to me from the President asking us to take on another issue. One is very short-term, one somewhat longer-term, which we 'll have to leave some time for discussion for also and that will occur at roughly 1:00 today. So at roughly 1:00, we will turn to the issue. This, of course, arises from the very well publicized and reported incidents not incidents, research results regarding stem cells and so on that we reported last week in just about all of the newspapers. And I just want to read the letter that I received from the President so that you 'll know what the task is in front of us this afternoon. The letter is as follows: "Dear Dr. Shapiro," and so on ... "this week 's report of the creation of an embryonic stem cell that is part human and part cow raises the most serious of ethical, medical and legal concerns. I am deeply troubled by this news of experiments involving the mingling of human and non-human species and am therefore requesting that the National Bioethics Advisory Commission consider the implications of such research at your meeting next week and report back to me as soon as possible. I recognize, however, that other kinds of stem cell research raise very different ethical issues while promising very significant medical benefits. Four years ago I issued a ban on the use of federal funds to create human embryos solely for research purposes. The ban was later broadened by Congress, which will prohibit any embryo research in the public sector. At that time, the benefits of human cell research were hypothetical, while the ethical concerns were immediate. Although the ethical issues have not diminished, it now appears that this research may have real potential for treating such devastating illnesses as cancer, heart disease, diabetes and Parkinson 's disease. With this in mind, I am also requesting the Commission undertake a thorough review of the issues associated with such human stem cell research balancing all ethical and medical considerations. I look forward to receiving your report on these important issues."

What this request means for us is two things. One, in the very short term, today and tomorrow, we have to mobilize ourselves so I can write a letter to the

President responding to the first aspect of what he raised here, that is, he referred to the embryonic stem cell, part human/part cow and so on the first part of that letter. That needs some type of immediate response from us. My proposal is that we, as I said before, turn to that at 1:00. We will try to have some briefing, perhaps by phone, from at least one scientist who is not on the Commission; we have some excellent scientists in this area and on the Commission. Then we will go to our own questions and try to evolve a I don't know if you want to call it a position at least a response. And then we will do some drafting of an actual response overnight in some way and then come back tomorrow and probably very quickly I hope by that time quickly approve it, because we don't have a lot of time for discussion here. I'd like to issue that response, as the President requested, as soon as possible.

There will then be a second part to our work. And although there is no deadline in this request, my ongoing assumption is that we should try to mobilize ourselves and give a response to the second issue within about six months. It is a very complex, extremely important issue. Some of you have served on panels that dealt with very similar issues before. But there's a lot more known now; there's a lot more to discuss than there was in 1994. For example, I think that was the year of the embryo panel in the Circuit Court. So we will have to think carefully about how we will mobilize ourselves for that effort how we will use other resources besides those sitting around this table and so on and so forth. But that we have a few days or weeks to do; we don't have to do that in the next day or so. So we will return to this overall issue later on this morning excuse me, early on this afternoon. This morning our primary and critical job is to finish our discussion regarding what we have shorthand referred to as a Capacity Report. That has to be accomplished between now and 11:30. This will be our final discussion on this report. I will take public testimony at 11:30.

Let me just indicate how I would propose we deal with the Capacity Report this morning. We will focus, as we did last time, only on Chapter 5, which are the recommendations themselves. And we will indeed focus only, so to speak, on the boldface recommendations that are there. Most of these we've already approved and are unchanged from when we did them, or at least, in some sense, only editorially changed. Some, however, reflect some considerable change because of the interaction that's taken place among us in the last month and because of the various public comments that we

received regarding people's views of these particular items. In addition to which some members of the Commission Jim and I think Trish had an extensive set of discussions regarding Eric, well, a bunch of you were there and that has occasioned some better focus on some of these recommendations. I'll turn to Jim to present those. I don't think that they are in any way different than what was intended in the current one, which is the question of getting the language a little more accurate. So I don't think those will develop any problems. So I'm going to begin in just a moment, just to go through these one by one. Those of you who have editorial suggestions of which there have to be many because I have many regarding any part of this text, either in Chapter 5 or in the earlier chapters, please get those to us within the next three days. If we get them within the next three days in writing, then there's a very good chance they will be incorporated in the final text. We have tried to be as responsive as possible to the many thoughtful inputs that we have received from commissioners, and obviously you won't find your comments reflected in every case because obviously we all didn't have quite the same idea. But I think we made every attempt to be as responsive as possible. Now we will, of course, allow for if any commissioner feels well, let me just talk directly about differences that may be avoidable, where people just might disagree. We will adopt these recommendations by majority vote as we did last time. If anyone feels sufficiently strongly that they wish to have some type of statement added to the report that expresses their particular different perspective on an issue, they are, of course, welcome to do that within the same three- or four-day deadline. Now the benefits of this report obviously, this is an advisory report. A lot depends on how persuasive the report is. And while consensus is not the highest order of the day because we don't want to just keep changing things until we have consensus, there is some advantage to being together on an issue regarding the persuasiveness of the report. And so while you are certainly welcome to have statements included as your own thoughts and consciences dictate, I ask you to think carefully about it because it would be very unfortunate if the report, as I do not expect, would be littered with such comments. I think neither their comments nor our recommendations would be as effective. But that's something each of you can decide on your own and handle whatever way you like. So before I begin turning to the recommendations themselves, let me see if Jim has anything he would like to add.

DR. JAMES F. CHILDRESS: Just a warm thank you for all of you who

participated in helping to revise and sharpen the recommendations, as well as the text itself. And so many contributed to that. I would like to single out just a couple of things that I thought were particularly important. Without slighting anyone's contribution, I thought the effort by Alta and Alex, among others, to get it together I thought that really helped move us forward. Then, the reordering of the recommendations, I thought and I think Alta and Eric and others were involved in that I thought that that helped a lot. And Kathy Hanna's role as an editor has been extremely vital. The discussion that several of us had in a public context with patients, subjects, families and researchers over the weekend did help us see when people were taking our report very seriously and they were areas where there were a few things to be sharpened and clarified, so a few points could come out of that discussion later.

DR. SHAPIRO: Thank you. Eric, do you have anything to add about this report itself right now?

DR. ERIC M. MESLIN: No, just to emphasize that written comments are far preferable to verbal ones. If you have marked up copies, commissioners, hand them to one of the staff who are here. It is much easier than trying to track it down later. We will be putting copies of the recommendations up on transparency for those who are here to help facilitate the discussion a little more. Plus there are some supplemental transparencies, all of which can be made available in hard copy to the public if they wish.

DR. SHAPIRO: Thank you very much. I think the reality is that whatever we receive in writing will be seriously incorporated if at all possible. What we receive as advice is likely to be forgotten, not because of any meanness of spirit, but just by the pressing time that we have to get this all accomplished. So let's just proceed directly to the first recommendation. I think we all have the same draft. In any case, it's on page 125 and we can put it up as a transparency just so members of the audience can see it. You're quite far back I don't know if it's going to help or not. I hope you have good eyesight.

**RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT  
MAY AFFECT DECISIONMAKING CAPACITY**

This is the recommendation regarding IRB membership. It is basically unchanged from the previous time we looked at this and approved it. There are, on lines 22 on page 125 and on line 3 of 126, some bracketed words. You see them up there as well, that says "or trusted friend." That is a question of whether that should be added or not. So Jim, let me turn to you first to see what comments you'd like to make.

DR. CHILDRESS: This somehow was added to the text and the brackets actually are suggestions that some of us have for moving it. This notion of trusted friend is important when you think about the LAR, but it's pretty hard to bring that in as a criterion for appointing someone to an IRB on this. And it just seemed to be something that was missing; it got stuck in the wrong place.

DR. SHAPIRO: That's fine. So if there is no objection, we'll just remove that. Does anybody have any other concerns regarding this recommendation they'd like to raise at this time? If not, we'll assume that's approved. Thank you very much.

Let's go on to Recommendation 2, and again, this is one of the newer recommendations. This is an idea that I think did help crystallize a lot of concerns that were around the table and gives us a mechanism, in my view, for dealing with issues that divided us last time. Because we were divided on a series of issues, at least in my judgment, this idea without speaking about every word here in this recommendation seemed to me to be a useful and thoughtful way to bring some of us, at least, together on this. Perhaps Jim, if you wouldn't mind, I'll just make an initial comment on this recommendation and see what other comments there are and see what the responses of the commissioners are. As I looked at this recommendation, first of all, in line 24 of page 127, which is under (a) in the recommendations, it talks about the prospect of substantial future benefits. I really much prefer "compelling" to "substantial" that's what the text says in the first instance. I think it's somewhat of a requirement. It's also the language, incidentally, used, for whatever it's worth, in the NIH embryo panel report also in dealing with issues similar to this obviously not in the same context. So I actually prefer the word "compelling." And in item 8 on this recommendation line 19, it talks about interventions that are likely to be of minimal risk. Then, in light of the studied

population, this might be more controversial. I myself thought that that added a lot of confusion and was not necessary. And just because I want to tell you honestly that I'm also concerned about relativizing these risks so people already at very high risks can be thought to take even more risks than others. So I'd like to judge if it's a minimal risk, it's a minimal risk. People will make their judgments, either investigators or IRBs will make their judgment. But it seemed clear to me we would make those changes. But Jim, I'd like to know what your response is.

DR. CHILDRESS: I'm comfortable with the recommendation, but there are some people....

DR. RHETAUGH G. DUMAS: I still have difficulty with the idea of utilizing people who cannot make decisions on their own and who will not gain any benefit from the research. And to have a panel to make that decision doesn't satisfy my concerns. It's a question of who really is going to offer up this person for research on behalf of the people and who will get no benefits. So having a panel doesn't satisfy my concerns there.

DR. SHAPIRO: Diane?

DR. DIANE SCOTT-JONES: I have some concerns about the language; I think the language should be made to be more precise and more conservative. The line that Harold referred to, line 24 on page 127, now says "substantial future benefit." I think when we use "benefit" we should always use the word "possible," because research doesn't guarantee a benefit. If it did, it would not be research. So I think whether it's "substantial" or "compelling," I think it should be "possible" instead of "future" benefit. It's understood that the benefit would be in the future, because it doesn't exist now, so it would have to be possible. And then on the next page, 128, that risk is reasonable in relation to this "important," I object to the word "important." It should be "possible" benefit. We should always make it clear that research may give us a benefit in the future. It is not inherently important or inherently beneficial. That is held out as a promise of the research. So I would recommend those changes in that one. And then farther down, in Recommendation (c), well, Harold's already said that. To eliminate that part of this that makes the risk conditional upon the particular study population, I think that must come out. And then the next one, (d), and I feel this a little

bit about 8 also, it appears that this panel is not only going to review research protocols, but will actually conduct research itself. And I believe that 's a tall order for a panel. In (d) it says that the panel is going to develop data on the attitudes of potential subjects and others toward research participation. But that 's a big huge research project, and I think that 's too much to invest in this panel that will already have an overwhelming task. I think it takes lightly the very daunting task of assessing attitudes of persons toward research participation. We have very little research on that. There have been some efforts just recently to do research on what people think about informed consent, but that kind of research is only beginning. And to give it to this panel I think is a big mistake. And then I have some complaints about, on the next page, page 129, the bracket that the panel should have members of the patient community that 's on line 2. I think we keep sliding back and forth in our language between people who are patients and people who are participants in research, and I think we keep sliding back and forth from research to giving therapy or treatment to people. The language must be cleaned up there. Patient community, in my mind, is inappropriate there, and I just believe a person who is a patient, a schizophrenic person is not going to be a strong and equal and contributing member to such a panel. I think we 're fooling ourselves if we think that 's going to happen.

DR. CHILDRESS: Can I just respond to the first on the language, if I could? It seems to me that we can handle the first change more easily, in line 24 on 127 by going to the prospect and talking about the possibility or something like that rather than making the change later in the sentence. Because the prospect would be a way we could get the possibility met. And the second change I very much affirm.

DR. ERIC J. CASSELL: And you would take out the word "future," right?

DR. CHILDRESS: I 'm sorry?

DR. CASSELL: And you would take out the word "future" because it 's inherent in the word "prospect"?

DR. CHILDRESS: I think the first comment you made is easily appropriate I think it does approve it. I didn 't understand the second one, which went over the top of the next page. Could I just....

DR. SHAPIRO: She and I talked about this a bit in passing, I think, at the meeting. It actually doesn't make any sense there as a term; it's not in relation to the importance, but in relation to the possible benefit. Larry?

DR. LAWRENCE H. MIIKE: Several things are off. First, since I was the one who suggested "substantial," I still defend "substantial" because we have two other conditions being imposed here: relative risk, and you cannot do this research except with a particular population under study. So I still defend "substantial." I don't know what your test would be for "compelling" that's an awfully hard burden to reach. So if we are going to be moving toward "compelling," I'd like to know what that word means. Second of all, I'd like...

DR. SHAPIRO: If you tell me what "substantial" means, I'll tell you what "compelling" means.

DR. LAWRENCE H. MIIKE: Okay. Actually, I think "substantial" okay. It's like beyond a reasonable doubt ... but in response to Rhetaugh. My understanding is that this is not being overlooked by a panel. All the other conditions apply. In other words, you will have a surrogate person who has decided beforehand, etc., etc. So I think there are those safeguards. And I agree with Diane that I mean, this panel has to have a very focused mission, and its mission should be approval of research and not get muddied into doing the actual research itself. That should be left to some other group.

DR. SHAPIRO: There's a number of people Carol, then Alta, then Bernie.

DR. CAROL GREIDER: I actually have a slightly unrelated point about this Recommendation 2, and that is in reading through all of this language, it wasn't clear to me how the protocols were going to be referred to RAPID. Maybe there is an idea about that, but at least in the language of the recommendations, it wasn't clear whether it is self-referral by the investigators doing the study, or referral from an IRB, or a combination of those. And if that could be clarified, that would help me a lot.

DR. SHAPIRO: My understanding was that it would be forwarded by the IRB.

DR. GREIDER: It wasn't in the language, though.

DR. THOMAS H. MURRAY: Since we put this as the second recommendation, I read this and I said that if I were not an IRB, I would have no idea of what circumstances I have to do this. It becomes more clear later in the recommendation.

DR. GREIDER: But could an investigator self-refer if an IRB...?

DR. SHAPIRO: I have my own answer to that, but we'll see what others say. Let's keep that question and we'll come back to it. Laurie?

MS. LAURIE M. FLYNN: First, I want to congratulate Alta and others for the thoughtfulness with which this section was developed. I think it is a great improvement in the draft and I very much appreciate what went into it. But a comment and a question. The comment goes back to the earlier concern on the top of page 129 about making certain that we had appropriate representation from the patient community, and I think the concern was expressed that we might not be able to find individuals with the significant disorders who would be able to provide the kind of aggressive participation that would be warranted. And I just want to reassure you that indeed such individuals exist. They exist in numbers. We have a number of these individuals on our board of directors. We have one who is today representing us at a large conference in Japan. These individuals with schizophrenia, bipolar disorder and other severe disorders are not without the potential to recover some of their function and indeed to be assertive. Believe me, we have them being assertive in our organization regularly, and I think we want to be sure that we have representatives of the patient community, the individuals themselves as well as those like myself who may be caregivers for such individuals who may not be as well recovered. So I just want to argue for keeping this here and recognizing that there's no substitute for that vigorous voice and that it's available and that it's available in numbers.

The question I have relates to the earlier discussion about whether this panel could take on the job of developing data and information. I certainly believe that that's a tremendously important function. I wonder if those who were thinking about this panel had any reference to other such bodies in mind or could explore whether this is better done in a separate locus or whether there was a reason to incorporate it into the

direct work of the panel.

DR. SHAPIRO: I myself have a view, but I'm going to wait until Alta speaks to it and then we'll come back. Bernie?

DR. BERNARD LO: I have a number of comments. First, I think this is important as a mechanism, as a procedure for trying to allow certain research to proceed which otherwise would not be permissible under the guidelines we now have. One point I'd like to make is that I share with Diane concerns about the language on line 24, 127 and flowing over. I'd like to try to bring us back to what I thought was the driving force behind it. It's not just any substantial future benefit. I thought we were really looking at studies that in the language of regulations for children promised the possibility, understanding the nature of the disease with which these persons were afflicted. So it's sort of getting at the basic science, the pathophysiology that would, in turn, enable future therapeutic developments. I would like to see some sort of recognition that we're trying to keep an eye out for research that will lead to a fundamentally better understanding of the very nature of the condition that's causing the mental impairment, because I think that's going to be helpful to IRBs and hopefully to this panel in deciding what counts. I agree with the concerns raised about giving this panel too much to do, and I think to ask it to collect data is really not feasible and not practical and we should do that under another guideline to NIH. Having said that, I think we do need to take into account how feasible this is going to be. I like the acronym RAPID, but I think it gives the promise that this is going to be a fast turnaround time, and I have exactly the opposite concern: that it's going to be slow getting off the ground, and if it gets off the ground, that it's going to be a slow deliberation. I would like to, other than just in the name, have some provisions there to try to make sure that an investigator who has a truly important project that promises to really substantially improve our fundamental understanding of the condition and doesn't pose a whole lot more than minimal risk is not going to be delayed for one or two years. I think the example you cite of only two protocols being submitted to bypass the current regulations has to give us reason to pause that this is going to be feasible. Now setting up a standing panel would certainly help, but I think by nature, this kind of centralized panel that only meets occasionally means there's going to be a possible long delay time building. I know you're trying to get around that by having the panel work on guidelines for all categories that the local IRBs can then implement.

But until that gets started, there is going to be some case-by-case review to get a better understanding of what categories make sense for broad exceptions. I think in that period we need to pay more attention to how to make this really work in an efficient way.

PROF. R. ALTA CHARO: Two quick global comments and then some specific language issues. First, I think Bernie's comments simply point out the fact that everything here is still an attempt to find some way through a fundamental tension that I think is exemplified by Bernie's desire to expeditiously permit research that goes to the fundamental nature of these diseases. And Rhetaugh's concern that as a matter of principle, it's inappropriate to be using people who can't consent for themselves to research that offers no personal, direct medical benefit from participation itself and has more than what we would call minimal risk. To Rhetaugh I would only respond that that is a principle that concerns me. It certainly has driven my discussions here, but I've come to peace with this kind of compromise because I see that there are issues not only of justice within a generation in which we say why are these people being used and not somebody else, but that there are questions of justice between generations and that all of us, whether competent at the moment or incompetent at the moment to make decisions, have been the beneficiaries of research in the past. And that we didn't ask to be beneficiaries, but we are and that this use of ourselves is an offering to the next generation. On this kind of inter-generational level, I can come to peace with this. It's imperfect, but that's how I've managed it.

On the specifics of how such a panel might work, the second global comment to Bernie is that whatever we don't manage to pull off here is going to wind up getting worked out within the government if the government decides to set this thing up, because it doesn't self-implement. Unlike some of our recommendations the IRBs can simply adopt, this panel would actually have to be created, staffed, given a room, given Xeroxes. So that there is going to be governmental involvement working out the details: things like the possibility of a deadline for its actions, must respond to a request within X number of days, things like that, might all get fought out. So that takes a little pressure off us in nailing down every last regulatory detail for this particular recommendation, although you might want to insist on certain things being put in there as guidelines for that. On specific language, in response to Diane's comments about 8 & (d) being tasks that may be beyond the panel because they are about data collection and

the reasons for the data collection, I think were discussed last time. It strikes me that it's possible we could take those out here and roll them into Recommendation 19, which is a suggestion to NIH to sponsor research on certain topics. These could easily be rolled in there. I could tell you historically that at the time that this particular section was being drafted, Recommendation 19 was not terribly well developed, or it wasn't somehow at the forefront of our minds. And it seemed important in the thinking of the panel about when it's appropriate to approve this research to have some guesstimate of the degree to which it's facilitating the actual desires of people who can't speak for themselves, or it's overruling them. That's why the question of attitudinal studies seems pertinent. But certainly it needs to be done by this kind of panel.

Finally, with regard to (a), if I'm understanding what I'm hearing, I wonder if I might try out some language to reflect what people have said at the table. Where it says lines 23 and 24 on page 127, "if the panel finds a protocol offers the prospect of substantial future benefit," to substitute instead "if the panel finds that a protocol offers the prospect of substantial improvements or compelling improvements," either one, in our understanding of the fundamental nature of the disorders that is prevalent within the population. And that its risk to subjects are reasonable in relation to this possible benefit. That might be language that we can work with. If not, keep going. Last, and my personal comment, there's something present in (b) that's been omitted from (a) that I would like to have put in there. On page 128, lines 12 through 15 state that "under no circumstance, however, should the panel promulgate guidelines permitting IRBs to hold subjects ... that reasonable people wouldn't participate in." That's not present in (a), where they're doing a protocol-by-protocol review, and I'd like to propose that it be there. And that therefore line 4 continue by saying "under no circumstance, however, should the panel approve a protocol that reasonable competent persons would decline to enter." Okay? And finally, on the last note Carol made, in terms of the way I think when we were discussing it at the last meeting the expectation was that IRBs that don't have a guideline covering a particular topic but it does fall in this greater than minimal risk, no prospect of personal, direct medical benefit could approve a protocol conditional upon further approval by this body. Thus, there would be no point for a PI to self-refer because his local IRB's prior approval is a condition for getting this board to look at it. I think this was the intent even if it's not clear and

obviously it should be made clear if you think that 's a good way to go.

DR. SHAPIRO: Okay. Tom, and then I want to start drawing this together to see which things we 're going to change.

DR. MURRAY: I hope to start this process by stating that, number one, we do need to say something, even if it 's referred to later, about the circumstances under which an IRB would refer to RAPID. That needs to be included. I don 't think that would be controversial. Number two, I want to congratulate Diane for identifying a possible problem with 8 & (d), the commandments we 're going to give this group. I think it would require a different kind of staffing. It 's a very compelling but difficult mission, and probably in order of magnitude more expensive to have a group that not only did reviews but also did research. So I think on the whole I believe it would be better to take 8 & (d) and move them to another part of the report. And the third is Alta 's recent effort to renew the language of part (a): I thought we had a good one going with replacing the word "prospect" with "possible." I don 't want to get into the middle of a debate over whether it 's "substantial" or "compelling," but I 'd go for shorter rather than longer. I thought we had a good one that Jim did actually sketch out I would go with the shorter one.

DR. SHAPIRO: Let me make some suggestions here, because I don 't want to spend there is the question raised by Rhetaugh, which Alta engaged in her response. I very much feel the way Alta does on this one, that this is an effort to bring us together in a sensible way on an issue on which we had disagreed on exactly the point that you raised, and so in that way I strongly support the general nature of this recommendation. Regarding the IRB review, that is under what circumstances should an IRB or, as some suggested under what circumstances an IRB may wish to forward us both I think that 's a good idea, but I think it ought to be incorporated in the text immediately following as opposed to in the recommendation itself. So Tom, if you could help us out by just developing a few sentences that would go in the text. That is important and helpful and we can just put it in the text following the recommendation. With respect to data collection, that is 8 and (d), I don 't have a strong opinion on whether it ought to be here or somewhere else. I think the notion is a very good one, that someone ought to be doing this. I had always interpreted this recommendation as in some sense having this panel sponsor these things as opposed to doing them individually

themselves. That the panel have people who are experts on data collection and so on is not something that I anticipated. But it does impact the budget, obviously. We'd need a different kind of staff, a different kind of expertise and so on. So I think it does make we could easily put it here as part of 19 as something encouraging NIH. That perhaps is the easiest and most rational, sensible thing to do on reflection. We could in the text associate it with 19 and point out that this would be input through the RAPID system and make the connection from 19 in the text back to here. So if there is no objection, what we'll do is we'll take 8 and (d), transfer them to later with some text that would follow that that would say, by the way, one of the users of this data would be RAPID. Other people may want to use it also, so I think it is important to get this data and we ought to find a place in the report. With respect to the recommendation, regarding making it appropriate or analogous to the last statement under (b) and putting it in (a), that obviously would not be guidelines in this case, but protocol or something.... Let me just see how I have no problem with that myself, but does anyone have any problem with that suggestion? Larry?

DR. MIKE: I think it's a little bit redundant given the second and third conditions already stated in (a), which is that risks to subjects are reasonable in relation to the proposed benefit. But basically, if we're going to include that, then I think we need to do some work crafting the other. It gets to be a little repetitious.

DR. SHAPIRO: How do other people feel about that? Rhetaugh?

DR. DUMAS: I like including it. It eases my concerns somewhat to include it in both places. Because lines 12 to 15 refer to promulgating guidelines up at the top, I think it refers to decisionmaking by the RAPID.

DR. SHAPIRO: Just see how other people feel on this so we'll know how to draft on this particular issue. David?

DR. DAVID R. COX: I'm in favor of including it, largely because of the point that you made, which is that for people who are at higher risk, it would be putting higher risks on top of them. So the more that we can do to balance that out with words, even though they may be slightly redundant, we're making the point that we really don't want to go above a certain point.

DR. SHAPIRO: Don't worry about exact language right now. How

many commissioners are in favor of adding some sentence like that to (a)? All right, we will add such a sentence to (a). Trish and then Bernie.

PROF. PATRICIA BACKLAR: I think that on 8 and (d), I think Diane is absolutely right in bringing this up. On the other hand, I think 8 and (d) are extremely important and we are very aware that this has inhibited our even being able to write this report as we would wish to. So I want to make sure that it is not hidden away at the back. Is it possible to have some reference in this section that it 's going to be dealt with?

DR. SHAPIRO: Well, let me make a suggestion in that regard. Let 's assume that in the text immediately following this recommendation it will talk about this coming up farther down and it will also tie it back when we get later on.

PROF. BACKLAR: That I understood you would, but I didn 't want to wait until I got to the end to find out about it.

DR. SHAPIRO: But we 'll do it here as well, so we 'll say, right after the recommendation I don 't know what the words are but that Recommendation X below deals with an important set of issues regarding information this panel will need to have available or something. I don 't want a hidden item, because I think it is important. Bernie?

DR. LO: I 'd like to suggest first that Alta 's statement that she said a couple of exchanges ago, with regard to how this is an intent to solve.... What you said, Alta, about all research builds upon the altruism of the previous participants, I think would be nice to include in the text. Second, I agree with your point that we can 't kind of write all the regulations for how this panel would operate. But I would like to see in the text again a guiding principle that the RAPID panel should act rapidly. And how that is to be worked out is up to the special people setting up, but that 's something that we really do have in mind. And even if they 're going to say no, I 'd rather they said no faster rather than dragging it out a while. And finally, with regard to the language again at the bottom of page 127, I would suggest we also look at the regs for children and see what words they use because that 's worked moderately well and we should at least see if we can borrow some of that.

DR. SHAPIRO: I 'm sorry to interrupt you; I apologize. On the issue of

speedy, rapid turnaround, I understand the issue and we ought to be able to say something, although I don't think so within the recommendation proper about the desire to have this. So it ought to be in the text somewhere because since I don't know exactly what kind of problem they're going to be facing speed may not always be a good idea. It might be a good idea in some cases and not good in other cases, depending on the difficulty of the problem they're facing. So I would not object at all to in the text that follows this to say something about our anticipation hope that this is done as expeditiously as possible, etc., etc. Again, I don't have the words. But Eric, would you make a note of that and make sure that that finds its way into the text that follows this recommendation? And Bernie, if you could, as I've requested from Tom and we're going to keep track of all these requests today if you can give us a few sentences, even later today or tomorrow, that would be extremely helpful. Trish?

PROF. BACKLAR: I just want to make sure that in the text that follows, on pages 130 and 95, I want to bring up something that Carol mentioned and I think is very significant. I do want us to start talking about patients and patients' families. I think that one can use words like the "population that's being followed," or "the population that's being studied," "members of the population" and so forth, that I do think we are constantly confusing the issue of clinical treatment with research. We use the word "patients."

DR. SHAPIRO: Can I ask some advice from the members of the Commission on, still, the text that follows and (d). There's one particular sentence in there which, every time I read it, I can't say what's bothering me about it, so I want to bring it up now. And that is the text that goes from lines 5 through 7, the sentence that begins, "A secretary should ensure...." I went everywhere from thinking it was redundant given what we'd already said to thinking it was not productive. Since, if we are trying to say that every possible point of view is going to be represented on this panel, we're making an impossible request. I think I understand what the view of this was, that we should have a variety of views here, and I'd certainly favor that. I think that's said in lines 1 through 4, when we talk about the different and so I actually would recommend that we drop the sentence, "The secretary should ensure..." because I don't if there is an objection to that, please certainly let me know. Yes Laurie?

MS. FLYNN: No, I appreciate that, and think that that would be helpful because I think it would be nearly impossible to implement this, and it could become extraordinarily problematic were we to attempt to do so.

DR. MURRAY: All right, now I'm confused because I just think it's redundant.

DR. SHAPIRO: Yes, it is redundant, I agree.

DR. SCOTT-JONES: It is redundant, but believe me, it could become difficult.

DR. SHAPIRO: All right, we won't argue that point. All right. Well, we've had some extremely useful discussions here.

DR. SHAPIRO: Bernie?

DR. LO: I agree that simpler is better, but I'm concerned if we're leaving out something when we delete the method. I think it is important to have an independent professional, but I thought part of our reason for talking about the method was that we want to have some assurance that it's done in a way that makes sense to the rest of the community as being consistent with good practice standards. But also that it addresses this vexing question we've been tossing around of where do you draw the cut point? And it seems to me, if we're going to start putting in some notion that the level which you say this person doesn't have to pass, that he's going to depend on the circumstances and the nature of the risks, then you want that spelled out explicitly, and not just to say, "well, as long as it's a qualified professional we feel okay." So I think there's some notion that it should be spelled out in the protocol: how you're going to deal with those tough situations Eric was talking about, not the ones at the extreme. And that that decisionmaking procedure should be consistent with good practice.

DR. CASSELL: Well, couldn't we do that in the text that follows that? I mean, make it clear in the text? Because it's difficult to keep it concise and address all of those points in the recommendation, but it's not difficult to address those points, which are important, in the language that follows.

DR. LO: Well, again, just sort of thinking about our IRBs, they're going to scan for the things they can easily pick up. But if it says, "How are we going to assess

capacity? We're going to appoint so-and-so, who's a qualified professional," I'd also want to make sure they see there's a category of "What methods will we use?" just as a quick screen.

DR. CASSELL: Well, I think if you go and read the literature of methods, you would be unhappy if somebody came in and said, "I want to use this method or that method." Because there is no method at the present time that will satisfy everybody. But there are beginning methods that people will start using, like Grissom and Applebaum's stuff but it isn't yet a method. They talk about it one way and write about it a different way when they're talking about the method itself. But what you're trying to get across is clearly that this can't be some casual person: "Well, he looks okay to me." What you're trying to get to is that this has to be a qualified professional means somebody who understands the problems of consent assessment and whatever methods are available. For one thing, we call for research into those methods later on. That's one of the things we ask for specifically. So we're making it clear that we want to go in that direction later on. We could say, "See Recommendation X."

DR. SHAPIRO: I mean, a lot of how one interprets these things depends on our individual responses to words, and what the term "qualified professional" means. Presumably, from Eric's perspective, it means someone who really knows how to distinguish a good method from a bad method, and won't certify the inappropriate method here. But Bernie's suggestion, if I understand it correctly, is that you would like to continue to incorporate, in the recommendation itself, something about method. I mean, I don't know quite what words we'd be willing to use, but you feel that that's pretty important.

DR. LO: Well, I think the worst thing of all in a protocol is that the investigator really hasn't thought about it, it's a blank in the protocol, and you just don't know.

DR. SHAPIRO: Right.

DR. LO: And I agree with Eric: you can put a lot of boilerplate in your protocol, and I'd rather have them at least take the trouble to do that than to just leave it totally unaddressed. I just think that if you think about how IRBs operate, and how investigators operate, they will look for the minimal if they're so inclined what do we

have to do? You know, the checklist approach.

DR. SHAPIRO: How do other people feel about this? Do you want to retain it? David?

DR. COX: I was actually a bit troubled by this in reading the public comments, too. And I come down where Eric is. I would personally feel that there's not a good scientific way of determining this right now in terms of protocols. On the other hand, if we don't tell people that they have to go out and try and do things, we'll never develop such a thing. So I really like the idea of not and I agree with what Bernie says, that people are going to look for the simple way out here. I think it's a mistake for us to imply that there is a way right now that we're all comfortable with. At the same time, I'd like people to try and do it anyway. So, I like the more general approach that Eric gives.

DR. SHAPIRO: Well, the language that Eric used substitutes the word "must" for "presumed," and that already raises it a level. And so maybe that is really a good place to be. That has the "must" instead of "presumed," and then it has the last sentence or the second sentence, which says there are exceptions to this. That is, you use your common sense. And maybe that's a useful way to set it down here. And we'll try to put something else in the text. Regarding Eric's language now, do you want to read your second sentence, Eric? Or somebody read it?

DR. MESLIN: The second thing?

DR. SHAPIRO: Yes.

DR. MESLIN: "An IRB should permit an investigator to forgo this procedure only if good reasons exist for using less formal methods of capacity assessment."

DR. SCOTT-JONES: I have a comment. The second sentence still retains in it the notion that the assessment is going to be by some formal method. In the first sentence as it reads now, the independent qualified professional could make a clinical judgment and not one that's using some standardized method.

DR. CASSELL: But that's a method.

DR. SCOTT-JONES: Pardon me?

DR. CASSELL: That ' s a method.

DR. SCOTT-JONES: But it would generally be considered less formal than something that is standardized.

DR. CASSELL: Well, that ' s the point.

DR. SCOTT-JONES: Well, if I could be allowed to get my question out, my question is, do we want to retain that? I ' d like...

DR. CASSELL: Thank you, Diane.

DR. SCOTT-JONES: I like the idea that it would not be a clinical judgment, but there would be some standard way that would be developed even though we don ' t have that now, and I ' m not sure quite how to do it. But if we let the second sentence stand, it implies that the qualified professional is using some formal method rather than clinical judgment.

DR. CHILDRESS: I think Diane ' s pointing to a real problem in this, with the tension between one and two as Eric has reworded them by retaining the implication about formal methods in part two, even though we haven ' t within part one.

DR. CASSELL: Tension is good, even if it isn ' t good.

DR. SHAPIRO: I think this is a good point. Let me just ask Diane a question. I really hadn ' t thought myself, in the first part, that we had some kind of standardized test, because those were simply not available yet. And so I didn ' t want to recommend anything that was impossible to deal with. But perhaps in the second sentence, because I think you ' re right to point out the distinction here. I think your point is well taken. That you can perhaps say something like, and I don ' t have Eric ' s words in front of me, but if the second sentence now reads, "An IRB should permit an investigator to forgo this procedure if good reasons exist."

DR. CASSELL: Oh, that does it.

DR. SCOTT-JONES: That ' s good.

DR. SHAPIRO: Because then you don ' t have to use "if good reasons

exist," period, then you just don't go through with the first set of procedures. So, allow me just to read it once again, Diane, because I want to make sure that we, that is, if we disagree, we know why we disagree. The first sentence that Eric has now is: "For research protocols that present greater than minimal risk, investigators must employ an independent qualified professional to assess the potential subject's capacity to consent." Then it would go, "An IRB should permit an investigator to forgo this procedure only if good reasons exist." That is, it allows you an out. And I have to agree that there's a fair amount I don't know how Jim feels about this, but there's a fair amount of leeway in here. And I think that leeway is required, because we just don't know enough about this.

DR. SCOTT-JONES: That's right.

DR. CHILDRESS: I guess the question would be what leeway is granted here. Let me just play the role of devil's advocate for a moment. What procedure is forgone? Well, we get a dependent rather than independent professional, or we get an unqualified rather than a qualified one. Those are the only two things identified in the previous part. So I guess I'm a little troubled about sort of where we were going with it.

DR. MURRAY: I like the rewrite, but I would add with due respect to Eric I would add, "... an independent qualified professional using an appropriate method." Because it gives the IRB at least two different things to focus on here. One is, is the professional independent and qualified? And two, what method are they going to use? The method might be clinical assessment. That's fine. But it might be some more formal instrument. And over time, I would like it if our recommendations were made relevant. And 25 years hence, there will be a terrific instrument that's psychometrically established. And we want to trigger using the best thing. So I think it's a reminder to the IRB: that's what method will be used. And I think that's appropriate.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I just want to raise another concern. And I raised it a long time ago when we were addressing this issue of capacity assessment. And that is, that it somehow implies that the giving of consent relies only on the internal capacity of the individual subject. But it relies on so much more. It relies on the complexity of the study itself; the way in which the investigator presents that information a lot of

investigators are very creative and thoughtful in presenting a study to potential participants in a way that is easy for them to understand; and the language somehow, at least the follow-up language, should recognize that there are many more elements to giving consent to research participation than the subject's capacity. Some subjects who have the capacity to consent will not be able to give true informed consent because researchers don't do a good job of presenting the study in language that is clear and accessible to a wide range of people. So there's another big problem that isn't addressed in Recommendation 8, and should at least be in the follow-up language.

DR. SHAPIRO: I certainly agree with the basic point, that all of the issues you've raised are very important, before one feels one has an ethically valid, informed consent. And perhaps we ought to consider where and if we have enough language in appropriate spots in this report to reflect that. We should perhaps refer to that in a few minutes. I can't bring the pages up to mind at the minute. There is quite a bit of stuff in the text about that. But this here recommendation, as I see it, deals with a part of the process, but only a part. And it deals with the issue of tries to deal with the issue of success in getting a recommendation being somewhat more careful in assessing capacity. That does not do away in any way with all the other important issues that you have raised. And I quite agree with you that those are very important issues, without which there is no valid informed consent, in my view. But let me Bernie, excuse me.

DR. LO: As I listen to the comments, it strikes me that many of you seem to be saying that there is no standardized method for assessing capacity that's widely accepted, which I agree with. And then, the inference you draw is that it doesn't make sense to try and force the investigators to specify how they're going to do it, because there's no standard method. I would argue the reverse: that it's precisely because there's no standard method that you want to force the investigator to think about it. "Well, I'm in a pickle. How am I going to do this? From the nature of my research, I'm going to have people whose decisionmaking capacity is going to be at least questionable." And rather than just saying, "I'll leave it up to this independent qualified professional," should the protocol and the investigator try and push a little more to say, "Well, how am I going to tackle that problem?" And I think it's that forcing them to think it through a little bit that often is the value of what an IRB forces.

DR. MURRAY: I take it that you support what I just recommended,

which is that we refer to a qualified independent professional employing an appropriate method. That 's what I noted.

DR. LO: Yes. If people are concerned about method, because it sounds like methodology....

DR. MURRAY: "Method" includes a psychiatrist 's consultation.

DR. CHILDRESS: We just ask them to indicate how the assessment will be performed, without using the language of method at all. It would be misleading.

DR. MURRAY: That 'd be fine. That 's right.

DR. SCOTT-JONES: I think that some version of what Jim is saying would be good: asking investigators to specify what method they use to assess capacity. And the capacity assessment could be made for this specific study. It doesn 't have to be an assessment of capacity for all studies of all kinds. And there are investigators who already do this. When they start to tell the participant about the study, they have a period where they let the subject reflect on that, and then they ask them to answer questions about the study that would show that they recall and understood what was told them. That 's a way to do it that would be specific to the study and would not require you to claim that you 'd assessed the capacity of the individual.

DR. SHAPIRO: I quite agree. That was my own interpretation of the program. It wasn 't that it was some standardized test somewhere.

DR. SCOTT-JONES: But I think most people would interpret it to be a standardized capacity assessment.

DR. MIIKE: But, Harold, the current language is in reference to the particular study.

DR. SHAPIRO: Yes. That 's right. So let me make a suggestion here. Eric, why don 't you and Bernie try to redraft 8, and anyone else who wants to participate, of course, can, with Eric. I want to deal with Recommendation 9 and then I want to take a break so that those of you who have assignments can work on them so we can put a chunk of this behind us.

DR. BRITO: Before you go on, I have a logistical concern. Regardless of

what we decide with Recommendation 8, the fact is that Recommendations 6 and maybe 7 precede Recommendation 8. First reading through this you're talking about Recommendation 6 you're already addressing the fact of whether a person is or is not capable of making their decisions. So I don't know if there we need to reference Recommendation 8, or just reverse the order. But it's just a concern.

DR. SHAPIRO: That's a good point.

DR. DUMAS: I have one word of caution in rewriting. As I hear the comments, there are some comments that would be instructions to investigators, which I think is inappropriate in the recommendation. I think that we have to exercise some restraint in how much detail we want to put in the recommendation. If we say "an appropriate method," that assumes that the IRB is going to ask for information from the investigator that will enable them to assess that.

DR. SHAPIRO: I think the recommendation we end up with will be no longer than the one that's here.

DR. DUMAS: Right.

DR. CHILDRESS: For those of you who are writing it, I think Eric gives us some structure to work on for that.

DR. SHAPIRO: Okay, let's go to Recommendation 9, and we'll go from there. Jim?

DR. CHILDRESS: The only suggestion I have follows our discussion of Recommendation 7. And it would be the last sentence, "The potential subject's dissent should, as always, have to be respected." Or the term that François Bellis proposed for our consideration, which was "heeded" rather than "respected." I don't have strong feelings there. But "honor" does pick us up another level, I think. So the proposal would be, "The potential subject's dissent should, as always, be respected."

DR. DUMAS: Right.

DR. SHAPIRO: Comments on 9? Okay, what I would like to propose to do now is, we have 20 minutes.

DR. SCOTT-JONES: Excuse me?

DR. SHAPIRO: Yes?

DR. SCOTT-JONES: There's a comment that we share over here. In Recommendation 9, we note a "conscious person." And it sort of suggests that in some of the other instances where we use the word "person," the person could have been not conscious. It just seems odd to have "conscious person" all of a sudden in Recommendation 9.

DR. CHILDRESS: I think you're right. That gets dealt with in the text, though, as to why we're to concentrate on the conscious person. And I agree it doesn't need to be in the recommendation.

DR. DUMAS: So take it out?

DR. MIKE: It just looks funny.

DR. DUMAS: It just seems odd. It jumps up at you, and it raises questions.

PROF. CHARO: You know, it always has been odd, but maybe the best thing to do then is in the text to make the exception that if somebody's unconscious, we do not expect the empty ritual of deciding from them. And that way we get rid of the problem.

DR. DUMAS: That's right.

DR. CHILDRESS: The text, I haven't gone back over it right now, but it does discuss that. And probably adding to it is good.

DR. SHAPIRO: Okay. We are running behind time, but we'll just have to do it. I'm determined to get this report done today. Let's take 20 minutes so those of you who are drafting are not taxed so much. But recommendations, let's have them back here in 20 minutes, at 10:30. Let's go.

Let me just announce a break in our agenda. It is really essential I've now reviewed all the changes that have been submitted. They all look to be in very good shape. We're going to try to get those typed out before we return because we're all going to have to read them out to you, so we can have something we can show you to make sure that the changes that we adopted to Recommendations 1 through 9 are, in

fact, the ones that we've agreed to. I'd like your concurrence with that. It really is essential that we finish going through this in the next hour and a half or, at the most, an hour and three quarters. We'll have to postpone public comment, unfortunately, because we really must get through this. So please, in our comments, let's keep that in mind. We're not trying to make the last and best little change in this; we're trying to address only matters of very considerable importance. So we've gone through Recommendations 1 through 9. We do have some particular comments with respect to Recommendations 15 and 16, which we'll come to in a minute. But let's now go and begin with Recommendation 10. Let me turn first of all to Jim to see if he has any additional comment on 10.

DR. CHILDRESS: Just a question about whether it might be useful to include, as we've done under some of the subsequent recommendations, a bottom line that would say and I think probably better not say our IRBs also comply with but rather investigators must also comply with 7 and 9.

PROF. BACKLAR: Eight and 9.

DR. CHILDRESS: We're reordering them now. That may be right, but 8 is really the one about assessing competence unless we reorder them, and I don't remember what number it would become now, but it's really 7 on dissent and 9 on notification.

DR. MESLIN: Okay well, we'll make sure we get the numbers right on that.

PROF. CHARO: One other small change here. I think it might just be a typo. On page 142, line 6: "the potential subject is given prospective authorization," delete the word "consent."

DR. SHAPIRO: Yes, I understand. Okay now I see; you're right.

PROF. BACKLAR: When we start with the legally authorized representative, talking about this, I would like to say right here that I feel quite strongly that that is a person who must be chosen by the prospective subject.

DR. SHAPIRO: Alta?

PROF. CHARO: I know that we've gone around this one and I know that I'm not going to be able to share Trish's insistence on this, and I wonder if this is something that just has to be voted on.

DR. SHAPIRO: Okay, what's your view?

PROF. CHARO: I think that as we've said in other places in the text and in my editing comments, emphasize more that potential subjects preferably will appoint somebody, but that if nobody has been appointed, the backup is a natural person who is authorized under law, which is going to generally be a relative. Sometimes it will be a friend, but will not be a bank or trust company or an institution of some sort.

DR. SHAPIRO: How do other people feel about this? We'll come to this again in Recommendation 16 when we've talked about legally authorized representatives, so maybe that's the best place to be.

PROF. BACKLAR: I just wanted to make the point here because we talk about this person and that's all I just wanted to establish where I'm going to become those are all going to be okay with me if that is so. And if not, I will have....

DR. SHAPIRO: That's reasonable, so let's revisit that when we get to Recommendation 16. Rhetaugh?

DR. DUMAS: I was just going to comment on you're leaving this one now? About the subjects choosing their own representative?

DR. SHAPIRO: We'll come back to that in Recommendation 16. Betty

MS. KRAMER: I have a comment. I think that the text that follows the recommendation is really confusing. The last sentence in the paragraph seems to conflict with the two previous sentences. To me, as I read it, it says if it's on the list then it's automatically minimal risk. And then the last sentence questions that: it says it might not be minimal risk. It may be a failure of understanding on my part, but I don't think it's clear.

DR. SHAPIRO: I think we can clarify that. I agree with you, I really do. Okay. Let's now move on to Recommendation 11. Jim?

DR. CHILDRESS: Here the addition of, again, rather than "IRBs" it

seems to me we should say that "the research must also comply with," and I would add Recommendations 7 to 8 and 9. And here 8 is relevant in that it's the one about assessment, because that comes into play only when we're dealing with greater than minimal risk and we have enough of that category now. So just add 7 to that as well and change "IRBs" to "research" or "the research must also comply."

DR. SHAPIRO: Carol?

DR. GREIDER: This is more general comment that will come up in a couple of other recommendations and it's about wording, but it may also have an issue behind it. And that is that I'd mentioned before my concern on the issue of therapeutic misconception when we use the term "research," that it has direct medical benefit. And although in Recommendation 11 it actually refers to the protocol, the wording above that on page 142 says "research involving greater than minimal risk." I would urge that we use the term "research protocols involving greater than minimal risk" to avoid this issue that research itself could actually be beneficial or not beneficial. And this will come up again in a couple of the other recommendations and I'll point them out when we come to them.

DR. SHAPIRO: That seems to me like a very helpful recommendation, so let's just adopt it and assume we'll make that change. It only clarifies and maybe in an important way. Tom?

DR. MURRAY: Two, I hope, quick things. I noted in the text that followed Recommendation 11, specifically in lines 22 and 23, which refers to the LAR must give permission and the subject must be given the opportunity to refuse. I guess we could use the language in 7. I think it makes sense and that is an important point to add that as a (d) under Recommendation 11. So at line 9 it becomes Recommendation 14, and (d) the subject does not consent.

DR. SHAPIRO: That's helpful. Let me also say that there is a condition missing in the text and that is, I believe, that the potential subject is given prospective authorization. That text, I think, if I read it correctly, never caught up with the change we made.

PROF. BACKLAR: Isn't that in line 6?

DR. SHAPIRO: Well, maybe it 's line 6. Yes, I 'm just talking about the text down below, in 21.

DR. MURRAY: I 'm referring to the language below. The point is, I 've noted in the language below, lines 22 and 23, that the point that was not included in the recommendation I just want to make sure it also gets mentioned.

DR. SHAPIRO: That 's right. I just wanted to since we were on line 22, I wasn 't really going to mention it, but it is missing the condition of prospective authorization to be consistent with that. But we 'll just add that in.

PROF. BACKLAR: I also am concerned, as Carol has stated, about this confusion about prospective benefit in a research protocol that is greater than minimal risk. And that one could have a very risky protocol that still offered a prospective benefit and one still might want it to go to RAPID. And I would be much happier with this recommendation if you had another condition, so (a), (b), (c) and then the possibility of going to RAPID, depending on how risky the protocol may be.

DR. SHAPIRO: Alta, then Laurie.

PROF. CHARO: Laurie and I may be having similar reactions on this one. To introduce now a new element in which the gradations of risk that are evaluated at the level of the local IRB may trigger a requirement to go to a national panel gets us into a very complex set of discussions about how one measures those gradations, how one gives guidance to the IRBs, etc. And I had thought that the fundamental problem with greater than minimal risk research arose specifically when the protocol offered no prospect of direct medical benefit. Where here there is the prospect of benefit, the IRBs, we have to do that balancing the way they do it all the time for all protocols, and would be happier if we kept it cleaner.

DR. SHAPIRO: I certainly agree with that. RAPID will have enough to do with the other protocols out there.

DR. MURRAY: This may be, I hope, quick. I would move that we strike the sentence on page 144, lines 1 and 2. It says that "dissent may be overridden only through a judicial process with full..." I thought we just had changed it. Would you say that? That the person who dissents from being in research, that always trumps? I don 't

know where this language about other subjects strike the sentence, is that okay?

DR. SHAPIRO: Okay. Let 's go along to Recommendation 12. Jim?

DR. CHILDRESS: Here, if I 'm not mistaken, under (d), that should be consistent with Recommendation 14, not 13. And then I would say at the end that research must also comply with Recommendations 7, 8 and 9. Just add 7 to that.

DR. SHAPIRO: Tom?

DR. MURRAY: I 'm sorry to be raising my hand so often here, but this is, based on my quick review of the document, this is the only recommendation under which RAPID is in fact formally evoked. First of all, am I correct about that? Second, I don 't know where letter (d) came from. That is, the protocol is approved conditionally upon approval by the RAPID panel. The notion of a kind of conditional maybe I just don 't know what it means. If it means what I think it means, it 's brand new and I 'm not sure why it 's here.

DR. SHAPIRO: I think because we 've not really addressed before, as someone else mentioned, the role of the IRB very clearly. This would be that the IRB could give conditional approval and then send it up.

PROF. CHARO: I don 't know how your IRB operates a case, but ours routinely will conditionally approve a protocol if certain changes are made consistent with the discussions. And so that language grew out of what was my personal experience on an IRB and its working practices.

DR. MURRAY: I understand, but maybe the language then could read like this: "the protocol is approved on the condition that the protocol also be approved by the RAPID panel." Just makes it a little clearer.

DR. LO: Number 12 I think is a tough issue and we 've had a lot of discussion on it. It continues to trouble me. As I think about the testimony from the two women in our last meeting, the woman who had a child with Fragile X and the woman who had a child with autism. Under current regulations for research on children, they would be permitted to consent to certain types of research that promised significant understanding of those conditions. So what we are doing now for parents of children with those conditions is cutting off research that is now permissible. It seems to me that

one can make an argument that for children it's different than for adults. First, because they have no opportunity ever to give prospective consent. But second, the relationship between parent and child is different from a relationship between an adult with mental illness and their family. Generally in this society we have the presumption that parents do act in their best interest, are given a lot of discretion and leeway. And I've been concerned about the types of research we're cutting off with our recommendations, while I understand the concerns that people who can't consent should not engage in research that does not offer the possibility of direct benefit to them. But I would just like to suggest that there was a compromise reached with regard to research on children that we are now undoing. And I wanted to suggest that for children with mental disorders that a protocol be designed to significantly increase our understanding of the condition, that we'll continue to allow the same kinds of approval that the current regulations for research on children allow. And that, it seems to me, would address at least the concerns of the two mothers who testified before us at the last meeting.

DR. SHAPIRO: Alta?

PROF. CHARO: Bernie, I understood from the text here and conversations last time that this report will not apply to research involving children and therefore will not trump the current rules governing pediatric research. What the text actually says I must confess I don't remember the exact page and line was that people can think about whether or not these could be used for children in the future but that the report specifically exempts that area.

DR. LO: That's fine, and I would just like to see that in this particular recommendation in the text.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I have a question about just the point that Alta made, because it was my understanding that what Alta just said is in fact correct: that the regs that apply to children that already exist will still be in force independently of what we say here. Because children with mental illnesses are still protected by the protections for children. But on the bottom of page 122, in footnote 254, it's not stated that directly. It states that those charged with reviewing and implementing the recommendations should consider whether they need to be modified when applied to

research with children. It seems to me that it should state that the regulations for children apply.

DR. SHAPIRO: I completely agree with you on that. Our position all along has been that this would not trump whatever regulations exist now with respect to children. And so that has to be clarified, and I thank you for pointing it out. Any other comments? Okay, thank you very much. Let 's go ahead to Recommendation 13. Jim?

DR. CHILDRESS: I had no proposed changes.

DR. SHAPIRO: Comments on Recommendation 13? Tom?

DR. MURRAY: A small change in line 12. It refers to general risks recommended. I think we should just leave the word "general," as specific risks may be more important than the general. I just think that it doesn 't do any work there.

DR. SHAPIRO: I agree; it doesn 't do much work there I agree with that comment. Trish?

PROF. BACKLAR: Well, I would like to see the word "specific" dropped because I believe that one could agree to be in a research protocol that was specific and you knew exactly what it was going to be, or you could give authorization to agree to be in research later and you could add limits or describe how it is you would want that research to be. So I 'm concerned about the "specific." I would like to leave it more open than that.

DR. CHILDRESS: That is in line 11, but be specific down below where we move toward considering degrees of specificity.

DR. SHAPIRO: Larry and then Laurie.

DR. MIKE: I would have to disagree. I thought that all of our discussions I seem to be repeating myself again I thought all our discussions about prospective authorization had in mind that fairly specific and close to the time of research, and we weren 't talking about two or three years out, maybe I 'd like to participate in that type of research.

DR. SHAPIRO: Let me just recall and remind everyone what our discussions were last time. We started off last time saying that it had to be a particular

research protocol, namely very tightly defined. And what this was an attempt to do was to broaden that concept, but not to broaden it too far. That was the attempt here. That's why this language is here. So by "specific," in this case it meant sort of a class, if you will, described. It didn't have to be exactly that protocol. And it goes on to try to say that if it's risk, benefits, etc., etc., it's been explained. So it's an attempt to look at a class of protocol, but not any research. So this was a compromise between those of us who wanted to say only a specific protocol versus those who want to say any research. This was an attempt to narrow that down. I don't want to defend the particular words, but the concept is very clear to me. You want to narrow it somewhat.

PROF. BACKLAR: I think this is because this kind of prospective authorization will be of particular interest to people who have early Alzheimer's and so forth. I think that most people with schizophrenia and bipolar disorders are going to be capable of making a decision about a research protocol that is immediate. So this really opens the door for people. Just as we agreed to give our organs out prospectively, we authorize this in the same kind of way.

DR. SHAPIRO: Alta, Laurie and Tom.

PROF. CHARO: Larry, I'd like to explain why I want a somewhat broader vision of this than you do. It's because it's not self-executing, like it is, with regular old informed consent.

DR. MIKE: I'm not saying I agree to broaden it, but I'm objecting to the dropping of the "specific" language, the word. I agree with what Harold said; I agree to broaden it to a class of research, but not so broad that it's just sort of like a general authorization.

PROF. CHARO: Then maybe it is just wordsmithing. What I would like people to do is to be able to say, "I'm willing to participate in pedigree studies and I've now come to understand what they are about. I want to be able to participate in imaging studies and I understand what they are about." I'm not sure which language you think accomplishes that. That's my personal goal in this recommendation.

DR. SHAPIRO: Laurie?

MS. FLYNN: Alta just made the comment, because that's the way I

understood it. Does it help at all if instead of saying a specific type of research, you talk about a category or class of research? Specific type makes me feel like we're going toward a rather tightly defined study, and I think we were trying to be one level up from that.

DR. MURRAY: I was trying to draft language that would be a little more precise here. Let me tell you what I have. This is section (h), page 145, lines 11 and 12, which now read "to a specific protocol or a particular type of research." I want to say....

MS. FLYNN: That seems very specific. That seems narrower than what....

DR. MURRAY: No, it's not, because it says "specific" protocol or a particular type of research. I heard both of those things, that people want to open it somewhat, but not open the barn door.

DR. SHAPIRO: Why don't you hold that language for a second, Tom, and we'll see some other comments here. Bernie?

DR. LO: Well, I think again it would be helpful to have the explanation is only three lines, and I think we need to have more explanation. I think what people are saying is that we want people to be able to consent, to give authorization as to more than just a specific protocol, but not to everything under the sun, and Alta gave a few specific examples. I think we should include that in the underlying explanation to help flesh it out a bit.

DR. SHAPIRO: I think the text is too short here I agree. Rhetaugh?

DR. DUMAS: What if we use the words "an area of research"? Would that broaden it enough and not too much?

DR. SHAPIRO: I have trouble with "area of research" because I'm really not sure of the type of protocol or the type of disease being studied and so on. It sounds to me, for those who are concerned about it being too broad, that goes too far. Let's return and see if Tom's language sorry, I apologize.

MS. KRAMER: Maybe we can take care of it by amplifying the text below it and say that the intent is to empower a person's autonomy and allow them to

describe what it is they want to consent to prospectively.

DR. SHAPIRO: Certainly, we'll add something that's a good suggestion.

DR. MURRAY: What I have, and with no particular pride of authorship in this lines 11 and 12 would now read: "... to prospective authorization to a specific protocol or a particular type of research." Now I include the specific protocol; maybe I don't need to include that. Because here I'm thinking of, I'm saying that when I'm demented, it would be okay to do this particular study on me. Now you can give consent at the time of the study, but that's why I thought you might give prospective authorization to such a study that could be done in the future or to a particular type of research.

DR. SHAPIRO: Well, what we certainly seem to be down to here is what we need to modify "type of research" with. And it's either "specific," for example, what's here, or "particular" I don't have a view on this myself. I'm not very particular on this issue, because it says direct benefits and all that could be in the same class.

MS. KRAMER: See if this would work: "...that can give prospective authorization to his/her participation in research if it's a direct benefit," and then add a sentence saying the intent is to empower the person to describe or to be as specific as I'm having trouble with the language.

DR. SHAPIRO: If you don't mind, I think I'd like to deal with intent in the text here. Because I really do not want just to come out, as someone can say, with a blank check. I think that's not feasible with what our discussions have been. So people have a view towards "specific" and "particular," that's really what we're down to here. Larry?

DR. MIKE: I feel comfortable with what Alta and what Laurie were saying, so maybe we're talking about particular classes instead of types.

DR. SHAPIRO: Let's go on to Recommendation 14. Jim?

DR. CHILDRESS: Okay, no suggestion, unless perhaps under (a), I

wouldn't have "done." Maybe we could change "done" to "chosen."

DR. SHAPIRO: The change that Jim recommended was in line 2 on page 146, to change the word "done" to "chosen." Other comments? Eric?

DR. CASSELL: Well, after all that care in Recommendation 13, the person has not given an authorization like that in anticipation of a specific study. But it doesn't matter, because the LAR distinctly heard that person say they wanted to be in that kind of a study and now they enter them into it. I mean, why make all the protection in 13 if you take all the protection away in 14?

PROF. CHARO: I think it's because when he gets to the recommendation, Eric, in enrolling people in research that's greater than minimal risk without benefit, we specifically make reference to prospective authorization. The LAR can't do it on his or her own. But with prospective authorization, right, you can.

DR. CASSELL: Does that mean that 14 applies only to minimal risk or greater than minimal risk?

DR. CHILDRESS: I think the point is that it applies only in conditions where the question is the benefit to them.

PROF. CHARO: It applies to research where the protocol offers the prospect of direct medical benefit to the subject, and it can apply to minimal risk research. All right? But if it's greater than minimal risk without the prospect of direct benefit, you're going to need prospective authorization in addition to the larger exercise of the assumption of authoritative powers.

DR. SHAPIRO: I think what Alta said is right, but I think we also need a sentence to correct, namely, that someone looking at just this recommendation who has not read all the previous work might get the wrong idea. So I think we need to correct the other recommendation. But I agree with your point that it can't stand as it is; we need to add something to put those together.

PROF. BACKLAR: And we did that before, which in fact we have a pattern of doing.

DR. CHILDRESS: That's a good point, but let's take one last look at

adding language to the recommendation to do that.

PROF. CHARO: Would that help?

DR. CASSELL: Yes, and (unintelligible).

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

DR. MURRAY: I have a different point.

DR. SHAPIRO: Let 's take, let 's let Tom make his point, if it 's easy.

DR. MURRAY: My point is that there appears to be an incompleteness in (a) in line 22 on page 146 that combines what it says in 16 and 19, where we 're talking about in choosing the LAR consistent with what the subject wanted, and we don 't always know that. It 's an inconsistent standard today. (Unintelligible.)

DR. MURRAY: I said Harold 's wonderful comments should be made part of the text after Recommendation 5.

DR. SHAPIRO: I don 't think I have any problem with that. Alta?

PROF. CHARO: I 'd like to propose the addition of a subpoint 8 that reintroduces something that has been present in previous drafts, where subpoint 8 says the LAR is a relative or friend of the subject. It accomplishes two things. First, it excludes institutional authorized representatives, which occasionally are appointed by courts for persons who are incompetent for legal purposes, and second, it further limits the scope to people who actually have a personal relationship. I think it goes partway to answering Trish 's concerns, not all the way, but I think that it gets rid of the worst possible misuses of this kind of mechanism.

DR. MURRAY: Could you repeat?

PROF. CHARO: It would be that on line 4, after the semicolon there would be the word "and," and then subpoint (c): the LAR is a relative or friend of the subject.

DR. CHILDRESS: But presumably no one would choose an LAR, make that choice of partner unless they were a friend or relative, but it 's possible. I guess the question is whether you want to open up the possibility that someone may choose

someone who 's not terribly close: a minister, rabbi or something.

PROF. CHARO: Oh, yes, I 'm so sorry. You 're quite right.

DR. SHAPIRO: If I could make a friendly suggestion here, I think I have the same concern that Jim just mentioned that if you want to add something here you could say the LAR is a mercenary appointed by the subject or relative or friend or something like that.

PROF. CHARO: Right.

DR. SHAPIRO: What then restrict it to a person...

PROF. CHARO: Yes.

DR. SHAPIRO: ...and their choice comes first. If they aren 't, if they hadn 't been chosen, then you go to a relative or friend.

PROF. CHARO: Right.

DR. SHAPIRO: I believe that accomplishes what you intended.

PROF. CHARO: Yep.

DR. SHAPIRO: And I think it 's consistent with some of the concerns Trish has.

PROF. CHARO: As long as they choose them themselves.

DR. SHAPIRO: Does that seem right, Trish?

PROF. BACKLAR: Yes, that 's...

DR. SHAPIRO: Okay. Thank you. Let 's go on to Recommendation 15. Jim has a recommendation about this recommendation.

DR. CHILDRESS: In thinking about this one during the time of the conference when you were all going over these very carefully, this one, as I recall, did not appear in this more than one of the previous drafts and so, as was commented at the time, we provided a moving target since some people referred to September drafts, some to October the 20th drafts, some to the new drafts, but I 'm not sure that this belongs at all in the recommendations. This seems to me to be guidance that ought to be relocated

in the guidance section. This is a different order than the others we had. Furthermore, the health care team, as someone pointed out in the discussion, suggested, again, a much more therapeutic model here than we would be comfortable with if we stick with this. If we put it in guidance, that should certainly be changed. And then, of course, there are confidentiality issues raised if we were to include this in Recommendation 2. So, I'd just recommend we incorporate this into the guidance section.

DR. SHAPIRO: (Unintelligible) explained, you had a comment about health care teams that you didn't get.

DR. CHILDRESS: But that having it the way we do here suggests again that we're connected much more to a therapeutic model that we've tried to get away from moving from patients to subjects in our discussion.

DR. SHAPIRO: And therefore?

DR. CHILDRESS: And therefore this is further, I think, supporting that kind of model we're trying to get away from and that whole recommendation does that. It could be incorporated in a different way and has done that.

DR. SHAPIRO: Laurie?

MS. FLYNN: I guess I want to disagree: I'd like to keep this. This has been an important recurring theme throughout the public testimony from families who have been involved in these settings. It is a large and pervasive problem with the psychiatric community in terms of keeping people involved, informed, and aware, given that families represent the ongoing daily caregiving entity in more than 60 percent of the cases and are often going to be involved in helping to make decisions or informing decisions about participation. I just think it's an important statement of the role that they have. The families are the ones who, as we've heard, deal with it when problems occur in the research setting, and very frequently they find a closed door when they want basic information about what's going on in the process. So I just want to say I think it's important. I think we've heard a lot about it and I would not be happy to lose it as a specific statement of the Commission.

DR. CHILDRESS: I forgot and just respond. I think it again is quite appropriate as guidance, but I would offer another reason for not including it here: if one

just looks at the recommendation, this really breaks the flow. It ' s a different order of recommendation.

MS. FLYNN: Where would it be if it were guidance? It would no longer have a number and would no longer be one of the 20-somethings....

DR. CHILDRESS: Right, but it makes a pretty important point about guidance for IRBs and institutions.

MS. FLYNN: It has a different force if it ' s guidance than if it ' s a recommendation and again, I have to say we ' ve heard from a great many people who felt greatly estranged from the process and greatly shut out of the kind of information that might have been helpful.

DR. SHAPIRO: I ' m going to recognize Larry in just a second. I think there are two issues here. One, should this be in a different place, that is, could it be another recommendation but not right here? And second is whether it should go under guidance and we could consider both going there and/or another alternative.

Larry?

DR. MIIKE: Yeah, I guess the compromise would be if you look at the title of this section, it ' s called "*Involving Subjects, Friends, and Relatives*" and then the recommendation, the wording itself, makes it a much more formal process. I think what you, what both sides are asking is that researchers be involved and to the extent possible friends and relatives, and to provide information but not the recognition as part of our health care team, which I think is what worries the people who are worried about this one. So the issue is involvement and information, so we should just state it as such.

DR. SHAPIRO: Eric? Excuse me, Tom?

DR. MURRAY: Did Alta wish to speak to him first?

DR. SHAPIRO: You can speak to him now.

DR. MURRAY: I hear what you say, Laurie. I understand that it must be very frustrating for a family to be excluded and not to be able to find out the more particular basic information about one of their relatives. Yet when I read this recommendation in this context and this language, I was quite alarmed because it reaches

way beyond research. There's nothing in the language that indicates it should be limited to research. I would prefer that we find another way of acknowledging the legitimacy of families' and friends' concerns for information without making a formal recommendation certainly not this language because you'd have to have something else before I'd close the books.

DR. SHAPIRO: Laurie?

MS. FLYNN: I appreciate the concern, and I appreciate the concern about linking it up to this health care team concept, but I guess I want to restate that we're talking now I mean, we've talked about the vulnerability in the population, the concern about their ongoing care and their ability to withstand the potential incentives and coerciveness in some of the research designs. We've heard from folks who might have been able to more appropriately participate had they been aware, and it just seems to me that if we took that seriously we would want to take the role of families and friends seriously. And we want to make a clear statement.

DR. MURRAY: I have an idea.

MS. FLYNN: Okay.

DR. MURRAY: It's a terrible idea, but it's that you're really talking here about legally authorized.

MS. FLYNN: Right.

DR. MURRAY: It's quite clear that the legally authorized representative offers whole whatever is relevant about the study and also about potential subjects, provisions that might make them reasonable or inappropriate subjects or not. So what about some locution to the investigators that they must provide a legally authorized representative overall?

PROF. BACKLAR: And you could put that into 14 because that's where you identify the legally authorized...

DR. MURRAY: And their confidentiality

PROF. BACKLAR: And the issue of the waiver of confidentiality and so on and so forth and etc.

DR. SHAPIRO: Excuse me; I lost track of this last interchange.

PROF. BACKLAR: I'm sorry, I'm sorry.

DR. SHAPIRO: So I'm not sure that I'm sure it is a brilliant idea. Let's see if it will work.

MS. FLYNN: In so doing, though, you narrow it only to circumstances where a legally authorized representative is involved, and in fact family caregivers are involved in many other ways and in research that doesn't include the use of legally authorized representatives. I mean, we're the folks who deal with this, you know, when the protocol is over.

DR. MURRAY: How do we do that consistent with respect to what the patients want known?

MS. FLYNN: We can talk about the patient's confidentiality. We can say "with permission of the patient." It's not even brought up. It's not even considered in many settings.

DR. SHAPIRO: Diane, and then I have a comment about this.

DR. SCOTT-JONES: I was wondering if it would resolve the issue if we just left out the reference to "health care team" wherever we end up with this statement. If we just say that, just make the point that investigators find ways to recognize, to involve family and friends of incapacitated subjects and to share appropriate information with them. If we leave out the reference to patients and health care teams, we're again talking about research, which is what we're focusing on. I think then we would get out of this problem of the health care team and the health care teams' obligations to families.

MS. FLYNN: Right.

DR. SHAPIRO: If I could make a recommendation: first of all, I do not think it belongs in this section. This section is about surrogate decisionmaking and so on and so, regardless of how we reform it, I think we need to place it. We can talk later about placing it in a number, let's say guidance, or if it's an actual recommendation. And I think, in my own sense of the discussion we've had in this area, is that we want these investigators to find ways to keep in communication with the most involved family

and friends, not every family, but the most involved family and friends. You're to share appropriate information with them. That's the gut of what we said and that's, we thought as we heard from testimony, something that many members of the public really had some concerns about. I think it needs to find a place in our report. So perhaps rather than the word "recognize," because that "recognize" to me is tied directly to health care teams, so you would have to use something other than "recognize," perhaps we could say "should find ways to keep in communication with the most involved family and friends of" I haven't gotten this all worked out in my head yet and to share appropriate information.

MS. FLYNN: Right, well, that's fine.

DR. SHAPIRO: And let's decide as we go along whether this comes in guidance or comes as a number X further on down the road.

MS. FLYNN: I appreciate those additions. I think they're valuable. Again, I would just point out that this becomes a protection. This is part of an important protection and again I would press for its being a numbered recommendation.

DR. SHAPIRO: We can come back and decide that, but Rhetaugh?

DR. DUMAS: I wanted to know what was seen as the significance of this statement about the protection and the welfare of the subjects from Laurie.

MS. FLYNN: The ongoing sharing of information and the availability of families to be part of the communication enables them to much better understand what's going on with their relative, how well their relative is doing. They can become involved in discussions with the research team and their relative about whether participation should continue. It's an early warning system that people are beginning to have a lot of problems. Families see way before anybody else does and sometimes before the individual, who may be somewhat impaired and can't see how they're doing.

DR. DUMAS: What about subjects who are estranged from family?

MS. FLYNN: Again, I'm fine if it's with permission of the subject. I'm concerned about those families that are providing care and are effectively shut out of any real communication or participation.

DR. DUMAS: All right. In that case, I would vote for this going in as guidance and have a statement saying that where it is essential to the welfare of the subjects and to the objectives of the research that this should be done.

DR. CASSELL: But doesn't that give too much leeway to the investigator?

MS. FLYNN: They're never going to think it's essential.

DR. DUMAS: I think it's guidance to them. Here we are talking about protecting human subjects and to the extent that this protection, that this communication with other people will aid and protect the subjects, then I'm all for it, but I think it needs to be made clear that this is a part of the effort to protect the safety and welfare of the subjects.

DR. SHAPIRO: I agree.

DR. CASSELL: No.

DR. SHAPIRO: Okay. I think that we're going to have to do some retraction here and try to incorporate some of these points and then come back to it and decide whether it goes in guidance or number X, whatever it is. Rhetaugh, do you want to take a chance at redrafting this? And then I think what we have agreed to, incidentally, is I think we've all agreed that it's part of the health care teams' definition, and we ought to eliminate that. The question, which I think is interesting, is whether we want to use language such as Rhetaugh has suggested and/or if we want to insist on approval by the subject, now, if it's approval by the subject, I certainly don't have any problem with that. I'm trying to think through in my head now, as we're thinking about this, what that means for a subject that's becoming incapacitated and therefore you throw them back into the kind of language that Rhetaugh was using. Trish?

PROF. BACKLAR: That way we would resolve all this if we let subjects pick their LARs. Maybe that goes right back into it; that's why I thought that the legally authorized representative is where this should be connected to, as Tom suggested.

DR. SHAPIRO: Let's try drafting, Rhetaugh, and see what we come up with here. Okay, Recommendation 16. Jim, I think, has a new recommendation for us. I

think it needs a new recommendation.

DR. CHILDRESS: And Jack Schwartz, one of our consultants on this project, has come up with some revised language for 16 and 17 and we have an overhead view of that because first of all there ' s 16, and there ' s another version of 17. We may want to get Jack up to say a few words about the proposal and then move into discussion.

MR. JACK SCHWARTZ: Well, the idea here is to capture two things. If you think about how states are going to react to the NBAC recommendation, some states will have legislation that addresses LARs for research and NBAC presumably wants to make a recommendation to the states as to what they should do in that legislation. But other states, probably the majority of states, will not take up this topic, and so in past discussions the Commission had provided an answer to the question, "well, if there ' s no legislation on research LARs, what should an investigator do?" And the answer was: rely on state laws about clinical decisionmaking authority. The attempt here is to capture both of those points. I think in the latest iteration, or previous iteration, it had gotten a bit lost. That ' s the objective of this language: to do both those things. And to incorporate the Commission ' s prior discussion about the value of having friends as well as next of kin, in appropriate circumstances, serve as LARs. I do not believe that, given our previous discussions, there ' s anything controversial about a big improvement.

DR. SHAPIRO: I thank you very much for that. It ' s really set up much better, but I don ' t believe it excuses anybody to us, although it certainly helps us to communicate an awful lot better. Larry?

DR. MIKE: I just have a question about the last part of I assume you ' re talking about 16. It says "by statute or judicial decision." I question that last part about "judicial decision," and I leave it up to the lawyers to say.

PROF. CHARO: But that ' s been supplanted by this.

DR. MIKE: Oh, I ' m sorry, I ' m sorry.

MR. SCHWARTZ: This does contain, though, a reference. In (b) there, states should confirm by statute or court decision, and that ' s a recognition of the

possibility that in some states, just as on the clinical side, courts rather than legislatures have identified.

DR. MIIKE: I like that we're going to confirm by statute instead of statutes.

DR. SHAPIRO: Oh, well, collect the honoraries. They're all the same for me.

DR. LO: I'm going to raise a question about the phrase "actively involved in the care," which comes up a lot. I think we're all assuming the dedicated loving family, but there also are relatives who are actively in the care in a negative way. I mean, clinically, we certainly won't let them experience it. Generally, in these kinds of LAR-type statutes, there's a best interest sort of condition. I'm just wondering: I think our intent is the beneficent family who has the best interest of the patient at heart, but the language doesn't necessarily reflect that. You could be involved in a very deleterious way.

DR. SHAPIRO: Jack, do you want to rate that?

MR. SCHWARTZ: It's a policy question for the Commission. That is to say, in my role in drafting this I picked up the active involvement concept that had been in prior evidence of the Commission's deliberation, and I had thought that the Commission had discussed it and opted for that. So I think that if the Commission wants to revisit it, then it would need a change in drafting, but that seems like a policy matter for the Commission, the extent to which there should be some reference to the degree or nature of the actual involvement. It is quite true that under some state laws there is no test for active involvement. It is the relationship alone that gives one the legal authority to make decisions, but many view that as not the right ethical outcome. That if there's a disconnect between the relative and the patient, no sense of values, no sense of connection, that that may not be the ethical decisionmaker but it is true, in most states, it would be the legal one.

DR. SHAPIRO: Alta, then Trish.

PROF. CHARO: Bernie, I don't think there's a solution to your problem because I can't imagine any way that one could write a rule that can distinguish

in the rule itself between the people that you want and the people that you don't. And this was an effort to minimize the possibility that you get people that you don't want. I think what is being referred to here is the situation where you've got a nephew who lives all the way across the country and he's never seen this person for a year or two years who suddenly comes in and has the authority to make decisions. And we've seen that in clinical hospital ethics committees a million times, and we just have to live with it. So this was an effort to at least get rid of that problem, but I don't know if we could perfect it any further.

DR. SHAPIRO: Trish, then Dave.

PROF. BACKLAR: Well, actually, I think it's very important to say "actively involved in," particularly in these kinds of cases I agree, even though I understand the problems that you're dealing with. But the thing that I'm still very concerned about I know everybody knows that I want people to choose this person, but I get upset again about the confusion between research and clinical treatment, which is written into this as though this is exactly the same kind of thing that's going to go on with clinical treatment. Because of this old problem, the kind of person who is appointed this way for end-of-life treatment or where somebody suddenly becomes incapacitated, is not dealing in research, they're usually dealing in clinical treatment, where the provider is only concerned about the patient in front of them. And this is so very different that we're going to open this up in a way in which people really will not understand the difference. We're actually feeding into the therapeutic misconception.

DR. CASSELL: Quite an alternative the way you put it, Trish. How would you avoid that?

PROF. BACKLAR: Well, you know how I would avoid it. I would let this happen only if people could choose who they wanted and they understood what they were doing to a certain extent.

DR. SHAPIRO: Why don't we also take a look, because I think it's relevant to this discussion. Let's look at the proposed change for 17 and come back and look at both of these, okay? Because I think it's relevant to exactly this point, and then David I know you wanted to speak, so let's see what David's comment is first.

DR. COX: But it's a big picture issue here. I mean, I actually accept Laurie's basic premise that families who are involved with the care of these individuals are there to help them, not to hurt them. And in fact, I think that the big-picture part of this is that the situation is that these people are closed out now more than they should be, because if they're not there, they can't protect them and help them. There are going to be situations where you'll have the rare situation where a family member isn't wanted, he causes trouble, but in the big picture we want to empower these family members that care more and that are involved, and that's the point I'd like to get across. So we're not going to be able to solve all of these problems. Now if people come down differently on that balance, I think that's really what we're talking about here. People should decide how they feel about that issue overall but we're not going to solve all things with simple words here.

DR. SHAPIRO: Okay. Let's look at 17 and come back to this.

MS. KRAMER: I've been looking as I've gone through this whole document about where the institutionalized get protected and in particular, you and I had a conversation about this at the last meeting. Institutionalized persons who have been abandoned, by families, by whomever, and I haven't found anyplace in this report where we address them. If I'm wrong I'd like somebody to point that out to me.

DR. SHAPIRO: Okay, that's an important issue.

MS. KRAMER: And if not, okay, but if not I wondered if this might be a good place to incorporate it.

DR. SHAPIRO: That's an important issue, but let's come back to that.

MS. KRAMER: All right.

DR. CHILDRESS: Okay, this is on Recommendation 17. There is a typo, obviously, on line 3. That "it" should be "if."

MS. KRAMER: They choose.

DR. CHILDRESS: Right. And it should be "choose," also. So let me read it the way you think it should be and I appreciate staff for rushing and typing these things this morning under difficult circumstances "States should enact legislation

necessary to ensure that persons are entitled, if they choose, to plan for future research participation and to designate the LAR of their choice."

DR. MESLIN: Just as a drafting.

DR. CASSELL: I like that, but you could take off "to designate the LAR of their choice." If you say "designate the LAR," that 's a choice.

MS. KRAMER: It should say to choose the LAR.

PROF. BACKLAR: To choose, yes, not designate. Choose.

DR. MURRAY: It should say to choose their LAR.

PROF. BACKLAR: I agree.

PROF. CHARO: So am I hearing this right? "States should enact legislation if necessary to ensure that persons are entitled to choose their LAR." Is that what you were all suggesting?

(Several people say no and some discussion going on.)

DR. SCOTT-JONES: Choose to plan.

PROF. BACKLAR: And to choose, and to choose their LAR, and to choose.

DR. MURRAY: State legislature, if necessary, to ensure that persons are entitled if they choose to plan for future research and participation, to choose their LAR. Good, Jim. The intent here then, is you 're going to have possibly two types of LARs: one for other decisionmaking and one specifically for research. Is that the point of this?

DR. MIKE: Well, because you 're asking states to enact legislation and so you 're asking them to enact legislation specifically in a research context if state, yeah.

PROF. CHARO: I 'm not sure they would have to do it the way you 're suggesting, Larry. If you combine the previous slide that we were showing from Jack 's redraft and this one, states will have to look at their own internal rules, case law statutes and the ideas to bring it in line. If they 've got a durable power, they commend the durable power. If they don 't have a durable power, they can write one that includes this.

If they want to have a separate one for LARs for research as opposed to clinical care they can do that, but the point simply is that based on the last slide, we are hoping that people who have been authorized to make decisions in a health care context will also be allowed to become the kind of person who can make decisions about research that has a prospect or protocol that has projected some benefit. And that in addition, we ensure overall, more than anything else, that people are never denied to specifically choose their identity and let states do it their own way.

DR. MIIKE: But I don't see it as a necessity to be very specific about their research setting, because if we're going to have an LAR by state statute that has the broad powers to do these, why do we need a specific recommendation on the research area in particular?

PROF. CHARO: Some states may choose to make a distinction. We also make distinctions about the kinds of LARs that we will tolerate in the research context.

DR. MIIKE: No, but that's what I'm getting at. Is that the point here, that we're worried about LARs who may be inappropriate in some people's estimation about making research decisions? I'm a little confused; all I'm asking is why are we now focusing on an LAR that is specifically in a research setting?

MS. FLYNN: Would that be the case where a family member who's involved in a next-of-kin relationship in the clinical care setting, but there may be a decision on the part of the individual to choose someone, a friend or someone not typically the next of kin, to be involved in the research decisionmaking? That could be a situation where they might have different individuals that they would entrust different levels of authority.

DR. MIIKE: What I don't if you look at the other recommendations, that we have all empowered that individual to do that?

DR. SHAPIRO: Power of the LAR?

DR. MIIKE: I'm sorry?

DR. SHAPIRO: I didn't understand your last comment, Larry.

DR. MIIKE: Well, I mean, I'm looking at all the previous, where we say

we authorize, a person can make a previous decision to get entered into research if they're out or can designate someone. Are we, again I ask the question, is this a necessary recommendation? Do I hear a yes?

DR. SHAPIRO: It seems to me, yes. Let me also turn to Jack in a moment, because what we're trying to do now is to define those people under state law who would qualify under these previous recommendations, circumstances.

MR. SCHWARTZ: That's right. Perhaps it's helpful to remember that one root of this problem is the present common rule, which refers to legally authorized representatives but doesn't say anything about who they are. So there's a general assumption, but it's not stated in the common rule that one looks to state law to answer this question: who are LARs for research? But state law provides, in general, poor answers to that question, so the purpose of this pair of recommendations and perhaps they could be folded into a single one is to add, to give guidance, the Commission giving guidance, its recommendations to those states that will take up the issue of LARs. They may be LARs for a number of purposes or states may decide to address research LARs in particular, and the Commission would give guidance under those circumstances but also to provide for the circumstance or discuss the circumstance where there is no state decision specific to research LARs. What then? And so the two things together try to answer those questions. Guidance to the states and guidance to investigators where there is no state law on research.

DR. MIKE: Can I just see the previous recommendation then?

MR. SCHWARTZ: Sure.

DR. SHAPIRO: It may be a good idea to put these into one regulation. Actually, that's a good suggestion: sort of meld and put together in ways that are appropriate 16 and 17.

MR. SCHWARTZ: They were drafted separately simply because the prior version was.

DR. SHAPIRO: Do you want to let that out?

DR. CHILDRESS: And the investigators should accept this LAR subject to the requirements under Recommendation 13: "a relative or friend of a potential

subject who is recognized under the law of the state where the research takes place as an LAR for purposes of clinical decisionmaking; (b) states should refer by statute" misspelling there "or court decision that one LAR, for purposes of clinical decisionmaking, may serve as an LAR for research, and friends as well as relatives may serve as both clinical and research LARs if they're actively involved in the care of the person who lacks the decisionmaking capacity."

DR. SHAPIRO: I like that.

DR. CHILDRESS: And if we put 17 under.

DR. SHAPIRO: Make a list.

PROF. CHARO: Turn it on its side.

DR. CHILDRESS: You can tell I didn't go to surgery in my bed.

DR. MIKE: Well, well, but basically the upshot of it all is that a general LAR can be you're asking the states to say that they can also do research decisions but you're also having a recommendation that there be an LAR specifically for research decisions. Yeah, I find that sort of a really complicated way of dealing with what might be a really small issue.

DR. SHAPIRO: There are two issues that you've identified here which commissioners have to be concerned about. One is the one that Trish raised: whether an LAR identified for clinical purposes could also be used if the state chose for research decisions. And the second issue that Larry raised: whether we want to make a recommendation to the states that they consider legislation or other methods of deciding that research LARs might be a separate class, a separate person. As I understand it, those are the issues we're trying to resolve here, so let's just focus on the first part of 16 just so we decide one way or another where we're going to come out. That is, I don't want to have to read it again but that's really a question of allowing the clinical LAR to use a quick character to also serve and ensure protocols. And I know Trish feels that's not appropriate.

PROF. BACKLAR: Well, my concern is that we are conflating these two and that it will be misleading to everybody who is going to be involved in it. They won't get it.

DR. SHAPIRO: Tom?

DR. MURRAY: The very language of 16 currently actually contains an ambiguity that reinforces that confusion, that it 's not clear what the final phrase on "purposes of clinical decisionmaking" modifies. So let me suggest just to reorder it so that now it would read, "investigator," blah, blah, "relative or friend of potential subject who is recognized for purposes of clinical decisionmaking as an LAR under the law of the state where the research takes place." The first time I read it I thought we were saying that we were going to recognize the research LARs as the clinical decisionmaker. We don ' t want to give that impression. That ' s just a small thing but it eliminates one ambiguity.

DR. SHAPIRO: Must be getting around late in the morning because do you want to repeat that, Tom?

DR. MURRAY: Just reordering. Right now it ' s ambiguous as to what the phrase "for purposes of clinical decisionmaking" modifies. So I ' m just going to reorganize it; it could have led me the first time I read it that we ' re making the research LAR the clinical decisionmaker for the subject. That ' s not what we intend. It may happen, but that ' s not required. So all we do is reorder things. I could repeat it or I could save time. Look, I ' d be happy to repeat it. Should I repeat it or go on? Okay.

DR. SHAPIRO: That ' s right.

DR. MURRAY: Okay: "Who is a relative or friend of the potential subject who is recognized for purposes of clinical decisionmaking as an LAR under the law of the state where the research takes place."

DR. SHAPIRO: That is an improvement. Thank you very much. But there is a substance to this issue so I want to focus on this issue now. We ' ll come to the other issues in a moment. The question is whether the commissioners are comfortable with that idea of an appropriate phrase. Let ' s have a showing of hands so I understand where people are.

PROF. BACKLAR: Only if the person was active.

DR. SHAPIRO: This one says, Trish, if I understand this, is that

someone is recognized under state law for this purpose, whatever the state law happens to be, can make the decision. We're just dealing with (a) at the moment, right? Now (b)....

PROF. BACKLAR: Extends that.

DR. SHAPIRO: ...talks about, again, the only issue that seemed to be separating us was the "actively involved" issue, whether we want to retain, under 2, "actively involved." Bernie addressed this issue and had certain views on it and others had other views. Now how do people feel about that aspect of Recommendation 16(b), 2? Just to make sure we get some of these issues behind us.

PROF. BACKLAR: Are we raising our hands for "actively involved?"

DR. SHAPIRO: Actively involved; it's retaining the "actively involved." There's been pluses and minuses. How many commissioners would like to retain "actively involved?" Six, ten, that passes.

DR. MIKE: What does it mean, because it just says "may?"

DR. SHAPIRO: Yeah, I understand. Let's go to 17.

DR. MURRAY: It now becomes redundant, doesn't it?

DR. SHAPIRO: I just wanted to, now let's see, look at 17 and see what this adds, if anything, to what we just...

DR. MURRAY: It provides the language better than the original.

DR. SHAPIRO: I think this with the revised language is not completely redundant. It first deals with existing state law, if I understand it. Jack, help me out here. Yeah; states that have no law in this respect would be Recommendation 17 or 16, sub (c). Or have I got this wrong?

MR. SCHWARTZ: No, that's right, or a way to put it is: what do you want states to do? Presumably one thing you want them to do is to empower individuals to choose their research LAR, which is not now the law in any state. That's what this addresses. So you want to underwrite the concept on which everybody agrees, including Trish, that people ought to have the right to choose their research LARs. This would be

state law that would underwrite that. But what if people don't choose their LARs? Then what happens? The second thing you want is state law that says what happens now and state law would say, under the prior slide, state law should say that if somebody has a relative who serves as a clinical LAR, that person can serve in that role for the kinds of research you're talking about on the research side. So I do not think it's redundant. It just addresses a slightly different subset of the problem.

DR. SHAPIRO: I agree with that. Could I ask a question? Is there any need in this recommendation to think of the LAR as a person, which I don't think is in this recommendation?

PROF. CHARO: Rather than an institution.

DR. SHAPIRO: Yeah, rather than an institution.

MR. SCHWARTZ: Yeah. I thought Alta's language earlier was intended to address that in a different recommendation. It is certainly true that under some circumstances state laws, well, it would be rare for clinical decisionmaking to pick an institution, but they might pick an office on aging or a local welfare office, so if you wanted to eliminate that, it could do it here but you could also do it in the prior language.

PROF. CHARO: I just handed to Eric the parallel language for Recommendation 14 as corrected by you, it's taken care of.

DR. SHAPIRO: We are assuming that whatever we write for 17 here will be a person instead of an institution.

PROF. CHARO: Yes. Or a natural person, if you want to be really legalistic.

DR. SHAPIRO: Thank you. I really appreciate this. That will come up later.

PROF. CHARO: As many people are categorized all the time.

DR. SHAPIRO: All right. I think that there are some typos that have to be fixed up, and let's get the "persons" in there, and then I think we'll understand where we are in this. Okay. Thank you very much. Let's go on then to Recommendation

18. Comments? Jim, do you have any comments?

DR. CHILDRESS: none.

DR. SHAPIRO: Any other comments regarding Recommendation 18?

PROF. BACKLAR: Oh, yes, there is. We don't say, it's not in the recommendation itself, but it's in the body of it. We don't make it at all clear. The first thing has to be that we educate about the difference between clinical treatment and research. That was completely neglected in that paragraph.

DR. SHAPIRO: Neglect that in the text? I think you're right.

DR. DUMAS: Did she say that we should say what we want them to do with this?

DR. SHAPIRO: No, she just wanted to make sure that the educational materials we were talking about included addressing the issue of the difference between research and clinical treatment.

DR. DUMAS: This seems to lack something in the recommendation. It says that they should develop or review their existing materials pertaining to research involving persons with mental disorders. For what reason? To bring them in line with the recommendation, or to ensure that they are appropriately preparing people to behave in this way? I think there's something else that's needed there.

DR. CASSELL: Needs a dependent clause.

DR. DUMAS: Just a line, huh?

DR. CASSELL: It needs a dependent clause.

DR. SHAPIRO: That's fine. I agree to that. Just like that was our intent.

DR. DUMAS: That's easy. In conformance with the recommendation?

DR. SHAPIRO: She's going to write it.

DR. DUMAS: Yeah, I could just tell you the sense is...

DR. SHAPIRO: Including a dependent clause here is quite necessary down here.

DR. DUMAS: In conformance with Recommendations 1 to 17.

DR. SHAPIRO: I think, in my own view of this, is that it's yes, but even if none of these recommendations was ever accepted or implemented, there is a continuing need for better education, understanding in these areas. I wouldn't want it tied only to these recommendations because this is a need regardless if all the rest of this happens or doesn't happen.

DR. DUMAS: Okay.

DR. SHAPIRO: Okay, and we will, just the item you raised also Trish. Now we're on Recommendation 19.

DR. CHILDRESS: And we had the addition brought over from Recommendation 4 that we developed this morning, 4(b), to include here. And also in discussion of that with Trish, we thought that maybe the addition of advanced planning as one of the areas to note that additional research should be conducted on best be put in.

DR. SHAPIRO: A question here is that Jim, and I don't want to hurt the subject to change that follow your introduction to discussions with Trish.

DR. CHILDRESS: Sorry about that. I was looking down at the time. But to include something about advance planning as one of the areas we'd like to have additional research done.

DR. MESLIN: Change the italicized as well as the body of the recommendation?

DR. CHILDRESS: This would be in the body of the recommendation, included before the "and."

DR. CASSELL: Well, I mean the recommendation could be changed considerably and made a lot better.

DR. CHILDRESS: A lot of unnecessary material, which we haven't done yet.

DR. CASSELL: Right.

DR. SHAPIRO: Eric?

DR. CASSELL: I think we could make this a lot shorter. "The National Institutes of Health should sponsor research to expand knowledge about decisionmaking capacity," comma, "the most comprehensive means for evaluating the capacity for consent and the best techniques for enhancing the informed consent process," period.

DR. SHAPIRO: Good. Alta and then Bernie.

PROF. CHARO: I have no problem with Eric's change of the existing language but I did want to clarify, based on Jim's introduction, that the two research tasks that were originally in Recommendation 2 for the RAPID panel would be incorporated now in Recommendation 19, so language was handed in during the break and then to ask a question, because Jim, you indicated that what had been 4(b), which was the request to IOM to do a study on the way in which placebo control, washout and provocation studies are done, you had indicated that it would be incorporated into 19 and I thought....

DR. SHAPIRO: Or a separate recommendation.

PROF. CHARO: Yeah. I just wanted to put in a bid to make it separate. I think that has been a real problem.

DR. SHAPIRO: Made a decision: Let's go back to the issue that's just been; Eric has language. Bernie?

DR. LO: This is such an why don't we finish that and then we can come back to my comments. I think this recommendation, which is to get the NIH to do pertinent research, is a good one and I accept Eric's editing. I think there's an opportunity here to urge the NIH to do even more. So in addition to sponsoring research, they do a lot of other things, including science grants, training grants, workshops, consensus conferences. I think I would like to see us encourage them to conduct activities in those spheres, pertinent to the topic of this report. Frankly, if the NIMH were to make a requirement for all their training grants and center grants that they have a component to help researchers learn and understand how to assess decisionmaking capacity and improve informed consent, which is different from the research arm, would go a long way toward improving the quality of practice.

DR. SHAPIRO: What your objective may achieve, Bernie, or would it be just giving it too short shrift to expand the word "research" and just say "sponsor research and other activities?"

DR. LO: If it provides room for the notion of center grants and training.

DR. SHAPIRO: I kind of like the idea.

DR. CASSELL: Yes.

DR. COX: I hate the idea. I'm willing to support that sentiment, but again this gets into implementing, or earmarking, what certain types of things... (unintelligible)

DR. SCOTT-JONES: But in some places the language is just redundant. It simply repeats what's already stated in the recommendations themselves. In particular, I have a comment about line 23 on page 129 where it's referring to the panel determining whether the research is exceptionally important. I think, again, we need to change the language so that it's more specific, because almost any researcher is going to argue that their research is exceptionally important. And I think it has to be specific to say that, something like the researcher must demonstrate that the specific study builds logically on existing findings or clearly builds on a solid body of existing research. I think we need not to use that type of language that's not specific to the kinds of decisions researchers would make when they're doing studies. But in general, in my view, it would be better if this were more concise, in the first place, this repeating after each of the recommendations.

DR. SHAPIRO: Diane, that sounds like a very good suggestion, but now you have an assignment. Could you help us out by writing it in the way you think it would be helpful? I'm really quite serious. We're going to have to...

DR. SCOTT-JONES: Okay.

DR. SHAPIRO: ...just share this around, because I'd like to be responsive and that would be extremely helpful to us. Eric?

DR. CASSELL: Well, the way it reads, it's the panel that determines whether the research is important or not, not the researcher, and that is the function of

the panel because that's what's being bounced against the rest of the subjects. That's the central core of the whole thing. The knowledge is more important than the protection of an individual subject the way they would be otherwise, and that's the panel's job.

DR. SCOTT-JONES: But my concern is that the panel not make just a global decision. One may have the view that this research is important, period; this kind of research is important, period. The decision should be made about the specific study. The panel should be asked to decide whether the specific study has some chance, based on the kind of decision that's made about research all the time: is it building clearly on existing findings? Science is incremental. It isn't just a judgment about the importance because, of course, the whole line of research is important in the first place. It needs to be to this specific study. Have you demonstrated that this particular study has a high probability of producing benefit in the future?

DR. SHAPIRO: Well, certainly this is a study-by-study review, but it would really be extremely helpful if you could just provide us with some suggestive language to deal with this conflict.

DR. SCOTT-JONES: Okay.

DR. MURRAY: This really is directed towards staff, if Jim and Carol are willing to take this instruction, that is. Diane's point reminds me that presumably the point of the text after the recommendation is explication. So we must be very careful to avoid anything that looks like we're making things more ambiguous or flatly contradictory. So a really careful concept-by-concept review of what's in that following language will be very important to those involved in this final draft. I also want to congratulate Harold on his brilliant implementation of one of the most successful principles of chairmanship namely, that is, you keep people quiet by making sure that every time that they speak they get some more work to do.

DR. SHAPIRO: Darn right.

DR. CHILDRESS: This is the best part of it, too. And since we'll be working on the text again in light of these changes in the recommendations, it is important for people to give us suggestions and hope the time frame within...

DR. SHAPIRO: Three days.

DR. CHILDRESS: Three days for text as well as anything else that needs to be considered. I have just two verbal points and then a query that came out of the meeting, the discussions with people from Baltimore the verbal ones, and I'll just mention them and their recommendations. On line 22 on page 127, rather than the IRB we need to just have IRBs since all of them may submit. And on 128, line 13, IRBs don't enroll subjects. They rather approve research that would enroll the subjects. So, I suggest we insert IRBs to approve research that would enroll the subjects.

MS. BETTE O. KRAMER: Say the place again? We didn't get the place.

DR. CHILDRESS: Page 128, line 13. Now the question that came up was whether RAPID, which drew some chuckles at the meeting, is too cute and whether that may in fact end up being detrimental to the recommendations rather than helpful. I just propose it. It came out of the meeting.

DR. SHAPIRO: Eric, then Alta.

DR. CASSELL: I mean, if we keep the acronym, do we have to keep "and," that funny "and" in there?

DR. SHAPIRO: Rather than research "with" persons?

DR. CASSELL: Yeah, on research "and" persons. Couldn't we say "with," and when somebody says how'd you get the acronym, we say that's the way it's spelled.

DR. SHAPIRO: Alta?

PROF. CHARO: Since I understand we will vote on these recommendations today even though there's going to be a great deal of editorial change in the text, I wanted to make sure that I understood the status of the language for page 127, line 24.

DR. SHAPIRO: Well, what I'm going to propose in the case of this particular recommendation is that we actually produce a new draft of this with some language today, now, this morning so that we can break in a little while. There may be some others like this. I hope not many.

PROF. CHARO: And then see a clean copy of the revised version?

DR. SHAPIRO: See a clean copy, right.

PROF. CHARO: May I just follow up very briefly then? To combine Diane's earlier point about how she would like, how she suggested this be written and Bernie's concerns. I wonder if I could suggest that the focus on the fundamental nature of the disease be something that might be in the text that follows the recommendation. That would allow us to maintain the shorter language in the main recommendation that talks about the prospect of propelling possible benefit and then talk about what those kinds of possible benefits would be in the text, if that might function as a solution?

DR. SHAPIRO: David?

DR. COX: This is exactly the point that I wanted to make. I think that the text is to give examples, but I support Eric's position, which is this panel is there to basically figure out what to do and we want to keep that as broad as possible. When we start narrowing and telling them exactly what they should be considering we're losing the whole point, so I'm very much in favor of keeping the actual regulations very broad but having good explanations in the text.

DR. SHAPIRO: Trish?

PROF. BACKLAR: I want to repeat again on page 130, line 5, when using the text that follows the recommendations once they say, even though I think we agree we're not going to use the word "patients," they say "former patients," and we all well know that many people with bipolar disease and schizophrenia are able to be, as it doesn't have to be a former patient, and including people with early Alzheimer's and so forth, so it's not a good idea to say "former patients."

DR. ARTURO BRITO: Sorry, a comment made earlier by Diane on page 129 at the very top, line 2, that hasn't been addressed is that of the research on the patient community. It should be changed to something on the order of "the potential research participants," in line with what Trish was just saying about the patient.

DR. DUMAS: What line again?

DR. BRITO: Line 2 on page 129. The RAPID panel should have

members equal to present the adverse interests of the potential research participants. That 's what we 're really talking about here. We don 't have to....

DR. SHAPIRO: Can I make a suggestion, Arturo, since despite the fact that you 're the host here today, you get to write that down. And let me make a suggestion that we leave this recommendation right now. I will ask when we break that perhaps Eric and Jim and Alta get together and try to assemble all these points and try to give us a new draft. Is that all right, Jim? We 'll do that at the break and come back to that.

DR. MIIKE: Harold?

DR. SHAPIRO: Yes?

DR. MIIKE: We haven 't addressed the issue of "substantial" versus "compelling" because if you write it in one way or the other, we 're going to disagree, so I guess we should decide that.

DR. SHAPIRO: All right. I favor "compelling."

DR. MIIKE: Done, and I want to disregard the fact that he 's the President of Princeton University.

DR. SHAPIRO: I think that 's a good idea also. I support that. I support the latter but not the former part. To settle it, since Larry 's requested, how many prefer "compelling" (pause to count votes); and "substantial" (pause to count votes)? Gotcha. Looks pretty even, doesn 't it? Let 's do that one more time.

PROF. CHARO: Shall we invent a new word?

DR. MURRAY: One of the problems is that you 're dealing both with probability and magnitude and you 're trying to just the way you estimate risk you know, how likely is it to have this particular outcome and how substantial and what magnitude they are.

DR. SHAPIRO: We 're trying to compress it to be simple.

DR. MURRAY: Oh, yeah.

DR. SHAPIRO: I used the word "compelling," really, following up from

what Alta has said before. I've tried to do something here that bridged some differences of views here on the committee and I thought of this as a more demanding task. That's how I thought it was going, Larry. It was just more demanding and I thought of that as a reasonable way to bridge the different views, but maybe that's my own. Maybe I'm hung up on the word "compelling." This is not a make-or-break issue for me. But I will break a tie if I have to.

DR. CHILDRESS: I'll break a tie the other way. Actually, building on what Tom's put in, I could change my vote and go with "substantial" because it seems to me that when we're talking about "compelling" we're talking about compelling evidence, we really are talking about something that does prove probability and magnitude of the outcome and that "substantial" makes more sense here. We're talking about the nature of the benefit. "Compelling" would make more sense if we were talking about how we'd put the probability and the magnitude together. Then we'd have "compelling" evidence. So I'd be inclined, for purposes of this particular formulation, to go in the "substantial" way.

DR. SHAPIRO: We're just going to vote on this and get it done with. I think we've all said. How many prefer "compelling?" One, two, three. "Substantial?" (Counting) Okay. It's "substantial." Let's get on with the drafting of this, okay? Let's go on to Recommendation 3, which is something we did approve last time as far as I know. As far as I recall, there's no change in the wording here, although anyone have any concerns with Recommendation 3? If not, I'll just proceed to Recommendation 4, where Jim has a change he would like me to read. All right, 3 is done. I want to now go to 4, where I think Jim would like to deal with both 4 and is going to recommend a 4(b), which of course we would have to then add 4(a) here. Let's not worry about that. First of all, let's deal with 4. Is that the one that's in our text?

DR. CHILDRESS: Yes.

PROF. CHARO: That's identical to the one we have.

DR. SHAPIRO: Yes, that's identical to the ones we have. Jim is going to suggest adding another condition.

DR. CHILDRESS: And this grew out of discussions several of us had,

including Jonathan Moreno, a former consultant, looking back to this particular report in the discussion we had in Baltimore. And clearly I don't know how many of you had the chance to see the *Boston Globe* articles, but the *Boston Globe* articles and the kind of discussions we had in Baltimore most of those discussions focused on provocation studies because of the particular problems they raised. And since we don't have a whole lot of evidence in this area about exactly what's going on, and since even the *Boston Globe* drew mainly on cases that we were already familiar with, Jonathan proposed for our consideration the following addition this would be 4(b) and let me just see if it's something that makes sense to people. It has a correction of that in that it requests that the Department of Health and Human Services IG, Dr. TK that they extend a challenge, and then the question is whether to concentrate on challenges to include washout research studies with subjects with mental disorders that may affect decisionmaking. Their actual and potential contributions to science, that is, possible contributions: the conditions of subjects who are the most compelling and critical for such studies and the methods ensuring the subject has the opportunity of obtaining subjects' consent.

DR. SHAPIRO: Bernie and Alta.

DR. LO: I think that's a good recommendation because these are the kinds of studies that really gave the greatest grounds for concern, and I think it's important to establish how widespread and what kinds of things are going on. I question whether the inspector general is the appropriate person to carry out that investigation. First, it kind of makes it into a police detection, quasi-punishment mode. And second, some of the things we're asking in this review are really scientific questions rather than investigatory questions. Again, I don't know if we want to propose specific bounties; I don't know if we want to have NIH set it up themselves, but one could think, for example, the IOM might be better suited to do a study. So I think the idea is terrific but I'm not sure if the IG is the best person.

DR. CHILDRESS: I'd actually accept that.

DR. SHAPIRO: Alta, was your comment the same?

PROF. CHARO: Everything Bernie has said.

MS. FLYNN: Same. Everything. I think the IOM would be a great place

for this.

DR. SHAPIRO: Jim, what do you think about the IOM for this purpose?

DR. CHILDRESS: It probably makes sense as a direction to go, and I certainly agree with the reservations that were expressed.

DR. SHAPIRO: Tom?

DR. MURRAY: I think that the principle is a good one. I think Bernie's comment about getting it away from a police action is absolutely on target. I also would urge us to use parallel language about the kinds of studies we're asking to have looked at here. But that's a different list, and people might interpret it differently than currently exists on the floor and I would just say keep the language....

DR. CHILDRESS: Consistency would be needed there.

DR. SHAPIRO: I take it there is....

PROF. BACKLAR: Does the language oh, excuse me, I'm sorry.

DR. SHAPIRO: I'm sorry, Trish. No, I apologize, please.

PROF. BACKLAR: The language that we have in 4 is also not quite accurate. I don't think one would want to put to randomize patients into placebo. Prof. Charo would want to say placebo trials. I don't think we're involved with the issues of randomization and control.

DR. MURRAY: Whatever word or language we use in the current 4 should be carried over into 4(b). That's all.

PROF. BACKLAR: With some alterations, is what I'm saying.

DR. MURRAY: What alterations?

PROF. BACKLAR: In 4, where it says to randomize patients. I would say to take out "randomize" and say placebo trials, studies to provoke symptoms, withdraw rapidly from therapies and placebo trials or otherwise expose subjects, etc., etc. So I can give you that language very quickly.

DR. SHAPIRO: Would it help you if instead of "randomize" it would be

to "enroll"?

PROF. CHARO: No, I think actually if you just replace it with to use placebo controls.

DR. SHAPIRO: Because we need to use something with a verb, too.

PROF. CHARO: Right. That's right. So if you say to use placebo controls I think probably you'll get what Trish is looking for.

PROF. BACKLAR: Right.

DR. SHAPIRO: Okay. Diane?

DR. SCOTT-JONES: If we're done with 4(b), I have a comment about 4 itself and it's simply to ask again that we not use the word "patient" instead of "subject" unless we have a reason for using "patients" there.

DR. MURRAY: Actually, they are patients because they're receiving therapies.

DR. SCOTT-JONES: But is it then necessary to call them patients in the part of the sentence that refers to placebos?

PROF. BACKLAR: No, we were....

DR. SCOTT-JONES: Because I think again it promotes the therapy...

PROF. BACKLAR: We were going to cut that out. We're cutting that out.

PROF. CHARO: Yeah, yeah, you can have your subjects there, Jim.

DR. SCOTT-JONES: I think "subjects" is still more appropriate because in this role they're in a study. They're not being given the best possible treatment for their disorder. In that sense, they're not patients in this context.

DR. MURRAY: And that's the only way they are not.

DR. SCOTT-JONES: But in this context, they're not.

DR. BRITO: I agree with Diane because it means here to withdraw

patients rapidly. I think we're talking about research subjects. I think this will have two effects and change the language throughout from "patients" to "research subjects" because we are focusing on these particular research subjects. Just because they're patients somewhere else. I think what we're adding to here is one of our bigger criticisms of this paper: it's the stigmatization, or potential stigmatization, and what we're saying here is that we're treating these people with mental disorders or decisionmaking difficulties as a particular group, but by changing over as research subjects, they have just become like anyone else that's involved in research. So I agree with Diane wholeheartedly here.

DR. DUMAS: I thought we had a convention early on that we would use the term "subjects"? Did I read that in a footnote somewhere? It's in the very beginning.

DR. SHAPIRO: I think in this recommendation it's very easy. The first sentence does use "subjects," and we just carry through with that, and the second sentence I think would be quite straightforward.

PROF. BACKLAR: I just want to make a suggestion about this, maybe throughout, and that is that we don't need to say "patients" anywhere. When they're not subjects, they're persons.

DR. SCOTT-JONES: And may I add a follow-up comment? In footnote 2 we say that but we don't stick to it throughout the whole report. We state that when they're in research they're going to be called "subjects" but when they're prospective research subjects, we're going to refer to them as "persons" but we haven't generally done that.

DR. SHAPIRO: That's a good point. We'll make those, and I appreciate that point. Very good. Very good. So I take it there is broad acceptance of both what would be 4(a), altered the way Diane has suggested is appropriate, and 4(b).

MS. FLYNN: Did I miss the discussions as to whether we were going to include all of those studies or just the studies that....

DR. SHAPIRO: No, we have to come to that. That's a very good point.

DR. CHILDRESS: As we move into that, one suggestion and I'll suggest the language here: impact request at DHHS, contract with the IOM to conduct the review. That would be the lead-in.

DR. SHAPIRO: There is the issue, Jim, as to how broad the assignment is under 4(b). The issue Laurie just raised. Do you want to put 4(b) back up there?

DR. CHILDRESS: Then that's why we put in two of those, (a) and (b). It's clear that it's challenge studies, provocation studies, that raise the most problems. Do we want to in their completion? What would be a good reason to ask for a good targeting study on those? On the other hand, the other, as suggested in the first part of the recommendation, 4(a) now, also raises important questions. I don't have strong feelings about it one way or the other.

DR. SHAPIRO: Let me just state a possible position on this. My experience in talking to people about this over the last months is that placebo controlled trials, for example, are broadly misunderstood. People have no idea intelligent people have not really, where this is not their area, it's not something they've thought through have a very hard time understanding what it is one's talking about. And so I would favor the rather broader scope here in the hope that an uncondensed report could really perform a very good education function for people. I could understand the other perspective, but let me just launch that as a possibility. Any concerns about that? Bernie?

DR. LO: I would also favor including placebo controlled studies, both for the reasons Carol indicated and also because they're regulatory concerns. And the FDA is loath to approve new anti-psychotic, antidepressant drugs without a placebo control trial, and so I think as long as that is operative you're going to be seeing a lot of pressures to do those studies even when there are effectively no treatments.

DR. SHAPIRO: That's a very good additional point. Now I think it's even more important that we do a broader one and I hadn't thought about that. That's a good point.

DR. CHILDRESS: There's also a question that Eric Meslin raised and I think it's a very appropriate one as to the placement. We, when Jonathan and I were talking about this, we were thinking about it as a way to deal with some of the issues

raised by the board. However, this issue needs to be placed under a new, broader version of 19 where we are talking about candid research that needs to be done. I think there were pretty good reasons, actually important probably to put in there. Actually put it into 19.

DR. MURRAY: In 19 instead of keeping it in 4.

DR. MESLIN: I think that a page could be made for that.

DR. SHAPIRO: What are people's views about that? I don't have a strong view on that.

PROF. BACKLAR: You'd take 4(b) out....

DR. MESLIN: Take 4(b) and put it in location 19.

DR. CHILDRESS: Where we're at, we're calling for research on consent. I would think that this would be another area of research we could....

PROF. CHARO: That makes good sense.

PROF. BACKLAR: That's good, yeah.

DR. SHAPIRO: So why don't we do that, Jim, if that is all right with you.

DR. MURRAY: I say this with trepidation, but we'd have to put the sentence and the description under 19.

PROF. BACKLAR: Yes, because I think this is a big concern to many people and I worry about us putting a lot of things into the 19 bucket, as it will be gone over and looked at as not so important because it's number 19.

DR. MESLIN: Just one organizational suggestion. It could be a separate recommendation to the IOM. It would become Recommendation 20, as it turns out. Recommendation 19 is research that we're recommending NIH conduct that could be used by RAPID. Recommendation 20 can be a recommendation to the IOM that will be useful to justify Recommendation 4.

DR. SHAPIRO: I think we want DHHS to request it from IOM whether it's a separate issue or not. But I think the point that Trish is making, if I understand it,

Trish, is that since we're dealing with this issue here, the text ought to forecast or send people's attention to whether it's 19 or 20 doesn't matter but send out attention....

PROF. BACKLAR: Right, that we consider it important and it should be considered.

DR. SHAPIRO: I think that's right. Okay, Bette.

MS. KRAMER: I would be happier if it stood as a recommendation on its own.

DR. SHAPIRO: That's fine. But let's put it back in that section. That's fine. I have no problem with that at all. I guess the biggest advantage of putting it on its own is of all the public comment we got, this is the most frequent.

MS. KRAMER: I would hate for it to look like we're constructing a catch-all recommendation at the end, sort of like providing education to the public. I don't want it to look like that, I mean, I want....

DR. SHAPIRO: Okay. That's okay.

PROF. BACKLAR: So could we have a vote on whether it should be up here under this?

DR. SHAPIRO: Absolutely.

PROF. BACKLAR: And go to the end because I'd like it as a "(b)."

DR. SHAPIRO: Okay. I sense we're ready to vote.

DR. CHILDRESS: I think the discussions indicated that it goes as a separate recommendation, that connective tissue will be present and perhaps even, well, there are many ways to do it, but you can highlight it up here in 4.

PROF. BACKLAR: Not just within the text after the recommendation but within the body of the recommendation? Is that what you're saying?

DR. MURRAY: Is it possible to put also "see also number 20," or whatever? We do that on other recommendations within the body of the recommendation refer.

DR. SHAPIRO: Does that seem satisfactory to people? Okay. Thank you very much. Jim, thank you for that change. It's been very helpful. Let's go now to Recommendation 5 and see what concerns any people have regarding Recommendation 5. Jim, do you have anything to add on Recommendation 5?

DR. CHILDRESS: I don't think I do. No.

DR. SHAPIRO: Anybody have any concerns about Recommendation 5? Okay. We'll go on. I'm sorry put your hand up high so I see you, Trish. I didn't mean to rush off. I'm sorry.

PROF. BACKLAR: I don't want to spend a lot of time on this because I know that we probably can't do it, but I want to make a statement that I'm concerned that we never did develop a series of scenarios so people would know what we're talking about and in a sense, I'm presuming, that that is what RAPID may do or who, wherever that went. Is that correct? Is somebody going to at some point develop a series of scenarios so you know where you go from minimal risk to much greater risk? Because I often find that when we're discussing this issue people have a completely different idea they had from one to another because we're not talking about the same issues. So when we look at this recommendation, it's so extremely abstract that we have great difficulty in knowing what we're talking about. It was very clear at this conference that we were at in the last few days.

DR. SHAPIRO: Alta?

PROF. CHARO: Trish, this recommendation actually does little but reiterate what's already in the federal regulations which in the end places the responsibility for determining if something is minimal or greater than minimal risk with the local IRB. But it is true that the RAPID panels' investigations, which have now been moved to Recommendation 19, included an effort to try and develop a consensus across the country over certain kinds of research and their likelihood of being minimal risk in most settings, with the local IRBs always, once again, tailoring it to the specific protocol they're reviewing and the specific population to be recruited. So some of that is still here. It's in a different recommendation but this is really nothing but a reiteration of the usual way research is reviewed now.

DR. SHAPIRO: Trish, can I ask a question? Because I was not completely clear what your concern was. This recommendation just asks people to be careful about evaluating risks and benefits. That 's what it says. And you were asking for scenarios that do what?

PROF. BACKLAR: I think that it would be extremely helpful if we had had an opportunity in the beginning we did discuss using scenarios....

DR. SHAPIRO: No.

PROF. BACKLAR: ...as an example of various levels of risk, and I think that an appendix that had a series of cases, scenarios, giving some kind of....

DR. SHAPIRO: Scenarios that would define this was minimal risk, this wasn ' t minimal risk, and so on.

PROF. BACKLAR: Right.

DR. SHAPIRO: I see. Okay. I understand.

PROF. BACKLAR: That took you down from low to high, because what I tried to explain is I often find that when we talk about this, I ' m talking about something quite different than you, for instance, that ' s all.

DR. SHAPIRO: Okay. Thank you.

PROF. BACKLAR: A casebook, almost.

DR. SHAPIRO: Okay. Anything else on Recommendation 5? Yes, Bette?

MS. KRAMER: I ' d like to go with what Trish is saying because I have a problem with this, and that is, is it really possible to make the establishment of minimal risk objective?

DR. DUMAS: I don ' t think so.

DR. SHAPIRO: We ' re going to get to issues of minimal and more than minimal risk in a moment.

MS. KRAMER: All right.

DR. SHAPIRO: So let ' s just keep that discussion for just a moment.

MS. KRAMER: Well, okay. Then it does reflect on the idea of putting out scenarios that weren't.

DR. SHAPIRO: We're not going to be able in the context of this report to do those scenarios because we just don't have time, but to do it may be an excellent idea. I think it is an excellent idea but we just won't be able to do. Let's keep to Recommendation 5. Yes, Diane.

DR. SCOTT-JONES: I have a question in light of the discussion that has just occurred about Recommendation 5 and Alta's point that this Recommendation 5 really doesn't say much more than is already existing in the current regulations. But are we then sort of burying the point that led to a lot of discussion among ourselves, which is in lines, I guess about 20 to 22, which is this notion of a three-tiered approach to risk is sort of buried in here. Is that why we have Recommendation 5? To go into a discussion of the levels of risk that caused us so much concern because it's here in this long explanatory text but it's not all reflected in Recommendation 5.

DR. SHAPIRO: That was not the purpose of Recommendation 5. The purpose of Recommendation 5 was simply a reminder about things that are really quite important in dealing with these individual reviews. It doesn't deal directly with minimal versus greater than minimal risk research, but if you read these protocols that we reviewed and I have seen, there are many protocols that do not follow Recommendation 5. Very simply, and yes, it's in the federal regulations, but the fact of the matter is there are many protocols I mean, out of the eight or 10 I looked at carefully, I would say six did not follow Recommendation 5, as simple as it seems. So it's just, that's the purpose of Recommendation 5.

MS. FLYNN: And I would agree it's important to restate it. I think it has value.

DR. SHAPIRO: It's not new. I agree.

DR. DUMAS: It's not new but it's very important to restate in this report.

DR. SHAPIRO: Bernie?

DR. LO: Harold, your comments of what you just said should be part of

the text under the, with the recommendations. I think it does provide a strong....

DR. SHAPIRO: We 'll try to I 'll try to write that.

DR. MESLIN: Okay, just let me make a note to myself to make sure I do that.

DR. CASSELL: I 'll make sure you do that.

DR. SHAPIRO: Okay. Let 's move on then: Recommendation 6. Jim, first let me turn to you to see if there 's any in black.

DR. CHILDRESS: I have nothing to propose.

DR. SHAPIRO: Eric?

DR. CASSELL: Well, I just want to make a change in the wording. The principle is there but it 's just not straightforward. First, those who have the capacity for consent may be enrolled in this study without his or her informed consent. The decisions of such persons about their participation may not be overridden by any third party.

DR. DUMAS: I like that. That sounds clear.

PROF. CHARO: Could you repeat it again?

DR. CASSELL: No person who has the capacity for consent may be enrolled in this study without his or her informed consent. The decisions of such persons about their participation may not be overridden by any third party.

DR. MURRAY: Sounds good.

PROF. BACKLAR: I like it.

DR. DUMAS: I like it too.

MS. FLYNN: Yes.

DR. SHAPIRO: Guess what, Eric? Guess what?

PROF. CHARO: Write it down.

DR. SHAPIRO: Trish?

PROF. BACKLAR: Yes, and because if you don 't do it like this, this

recommendation has opened a big loophole because it said without involvement with any third parties. It means that maybe there's not going to be any other kind of protection and many people, as we well know, are going to be able to consent to be in a protocol. Many people with schizophrenia, many people with bipolar disease, people with early Alzheimer's and in certain people with early dementia are going to be able to consent, and if you don't write it as Eric so exquisitely rewrote it, you will be in big trouble. We will be in big trouble. So, good. That does it.

DR. SHAPIRO: Okay. Eric will rewrite that. If anyone has any issue with that, we're clear on the idea here and so it's just a matter of language. Okay. Let's go on to Recommendation 7, where I know Jim has some changes he would like to recommend to us.

DR. CHILDRESS: This recommendation, I think, is involved in ways that actually causes us to lose the point we're making, and this particular recommendation was subjected to a rigorous philosophical analysis and critique at the Baltimore meeting and I think it was actually right on target. So let me just make a few preliminary points and then propose something that I talked about with a couple of people after that meeting that I think goes back and captures our initial formulation because the basic idea was that if anyone consents, whether he or she is competent or not, if that person doesn't consent we have to stop the research on that person. But the way this has evolved, with that including the language of choice, honoring that choice, in one formulation refusal which is a principle that Laurie pointed out brings in the notion of respect for autonomy in a full-blown sense. But we're actually in this recommendation respecting non-autonomous people and their consent for participation.

MS. FLYNN: Right.

DR. CHILDRESS: And so the proposed revision, which actually cools some of the language that's already in the text but not in the recommendation, is an effort to try to capture that. And it's that consent by potential or actual subjects must be respected regardless of the level of risk or potential benefit and the person's capacity for decisionmaking. And then the second sentence would remain the same as it appears in the text on page 138, with the exception that chose not to participate and chose to withdraw from a study. And again, that assumes, that seems to suggest full-blown

capacity for doing that. That would just be changed to previously dissented. So it would maybe approach people who previously dissented to ascertain whether they've changed their mind.

MS. FLYNN: I like this approach.

DR. SHAPIRO: Let's focus on the bold print up there and make sure it's the right view. I think, my interpretation is, it's exactly what we've had in mind all along, but let's just look at it carefully to make sure that we agree. And again, for those of you who have bad eyes, I'll just read it out loud once again if you don't mind: Dissent by a potential or actual subject must be respected regardless of the level of risk or potential benefit to the person's capacity for decisionmaking. That comes with the simple notion that we dislike the image of forcing someone who consented regardless of their capacity to participate in the research program.

DR. MURRAY: It leaves open what I imagine would be kind of a difficult job: just figuring out what counts as dissent for a particular person under particular circumstances. But I don't know any way around that. I suppose we have to just encourage, reviewers and investigators that they are to give this a fairly broad reading. Anything that looks like dissent or unaccountable consent.

PROF. BACKLAR: Well, maybe one wants to put that.

DR. MURRAY: Pardon, Trish?

PROF. BACKLAR: One may want to put that in the text that follows. I think that's very important and I think that if it quacks like a duck...

DR. MURRAY: Must be treated as if it were a duck, right.

DR. SHAPIRO: Any other comments? Okay. Well, that will be our Recommendation number 7.

MS. KRAMER: Excuse me, can I comment on the second sentence?

DR. SHAPIRO: Sure.

MS. KRAMER: I like the second sentence the way it's currently written. I like it spelled out very explicitly that it's both people that chose to participate

originally or chose to withdraw.

DR. CHILDRESS: Reintroducing the language of choice is again to build in a model that a person is actually competent and capable, and we're trying to cast the net more widely here.

MS. KRAMER: Okay.

DR. CHILDRESS: Capture even those who don't have the capacity, but they're resisting the studies and the problems of definition that comes with it.

PROF. BACKLAR: And also opens to the kind of loophole that Alta talked about, where the investigator would go back to assess capacity presuming that it's a person saying no, they don't have capacity. If they do, they have capacity.

DR. CHILDRESS: Okay. All right.

PROF. BACKLAR: The people who have mental disorders. Thank you.

DR. CHILDRESS: And that was just one example of our recommendation being taken seriously and subjected to very rigorous analysis and I say a useful experience.

DR. SHAPIRO: Thank you. Let's go on now to Recommendation 8, which begins by recommending certain protocols greater than minimal risk and so on. This has to do with capacity here. Jim?

DR. CHILDRESS: I have one word in brackets for further discussion since there's been some debate in e-mail exchanges about that. But let me start by raising some of the issues that came out in the discussion at Baltimore, as well as others on this particular one, and I'm sure that Trish and others, Diane and others who were there, Eric, may have some comments too. The big question is whether we want the independent formal assessment: under what circumstances do we want that? We said for greater than minimal risk. Okay? And then in the second sentence we say that there can be persuasive grounds for using less formal methods: an investigator may be able to present those to an IRB and that's where the IOM is going to be very critical for determining the latitude here. But some at the Baltimore meeting proposed that we really need to take more seriously a sliding scale, not simply a greater than minimal risk versus

minimal risk for the implication. Some others would say that this is just too broad for all mental disorders even though there may be a low probability that a person within that category would need to have capacity assessed. I mention those as the kinds of concerns. I don't think we can address all of them and properly respond to them but I think it's useful at this point as we nail this one down to at least have those in mind.

DR. SHAPIRO: Eric?

DR. CASSELL: This is a central problem. It's the thing that's raised a lot of concern among the psychiatric community and with investigators because they know very well it's going to make problems for them. But on the other hand, I must say that I think that an IRB should presume that the study will need to employ an independent qualified professional to assess. I don't think the words "appropriate method" go in there because I think what's going to happen is some tool will get generated and everybody will agree that tool is it. You pass it, you get consent, and all the business about the consent being a process, not an event, and all that will go by the board. Besides which, in many studies somebody who knows what they're doing can make that assessment that the person has capacity very fast and the assessment that the person hasn't got capacity on the broad scale. It's the in-between subject where somebody has to take time. And a particular method I don't think is the point. It's the professional that counts, not the method the professional uses. Now Doctors Grissom and Applebaum, in their book, make it clear that it does not have to be a psychiatrist doing this. They talk about any physician can do this and so forth. They make it very clear that it can be done and also and their instrument, which is not really a method although they call it that could be used by any person who's line of work that was. I don't think "method" should stay in. I guess that's the long and the short of it and I do think "only" should stay in. "Only" on persuasive grounds.

DR. SHAPIRO: Larry and Alta.

DR. MIKE: Ordinarily I don't comment on wordsmithing but this one sort of bothers me. It's got too many words in it. If an IRB should presume that a study would, basically we're sort of saying our studies should have these things in and an IRB "and," that "and." What is the point of putting "persuasive" in front of "grounds?" I don't know. Generally, I think our recommendations are just too long and wordy and

this one just seems to add some unnecessary words to it.

DR. CASSELL: I agree with that.

DR. SHAPIRO: Alta, Trish.

PROF. CHARO: I think that in the end, whatever words we use and personally, I have a problem with taking out "persuasive;" I would like to see taken out "only" but take out "persuasive" and leave in "only," that's fine too I think I'd like to help. I'd like to visualize this as a tennis match in the IRB reviewing room because I think the goal here is to make this clear enough that everybody knows what their jobs are. And I think we start with the understanding that even within the population of people who have a mental disorder, a very large number are going to be completely capable of making decisions for themselves. But at the same time, we start with the fact that in that population you'll have a higher frequency of incapacity than you would in the general population, so that what you want to do is have a tennis match that begins with the IRB going, here's a study that involves mental disorders. Does it appropriately handle the question of capacity? Which bounces it to PI to say yes, because we're employing a method or no, because we don't need a method because this particular population is made up of bulimics who may have a mental disorder but not one that affects decisionmaking. Right? At least with regard to participation in studies. And then the IRB says fine, but it's kind of a back-and-forth in terms of responsibilities, all of which completely invisible ultimately the subjects that are enrolled because it's all handled in the IRB room and nobody's ever insulted when there's a demand for a capacity assessment.

MS. FLYNN: Is that the way we think this is really going to operate? Because that makes me feel much more comfortable.

PROF. CHARO: Well, that was my understanding of the goal of the language. If it's not accomplishing that, let's keep wordsmithing. But that was my understanding of the goal of the language.

PROF. BACKLAR: That makes me very comfortable.

DR. SHAPIRO: It seems to me that Trish, I'm sorry. You don't mind me for a second. That we wanted, our previous discussion indicated that we wanted, for

the subjects at greater than minimal risk, for IRBs to ask themselves the question, "What about capacity assessment?" And then it would be up to, that's capacity assessment administered, etc., whatever we decide to say about that. Then it would be up to the investigator to say if there are reasons, persuasive or not I mean I don't know what words we should use there that that is not necessary in this case, then it's not necessary. I would not feel comfortable with this recommendation without the second sentence or the second sentence somehow articulated. I'm not tied to particular language here on either side, but it was on that idea as to greater than minimal risk protocols, we want this issue raised and responded to in ways that satisfy the IRB.

PROF. CHARO: May I suggest alternative language there?

DR. SHAPIRO: Let Trish go first.

PROF. BACKLAR: I do think that the issue here is this sliding scale issue, and I would like to see some language I'm not certain that I would do it but I would like to discuss it with you that in the qualifying sentence that follows the statement that one would get at that concept of the issue of the sliding scale. I think that would make almost everybody happy with all the comments we got back, including the American Geriatrics Society, which had a very thoughtful paragraph about this. I think that would help them out too.

DR. SHAPIRO: Eric?

DR. CASSELL: I'm sorry?

DR. SHAPIRO: Did you want to speak?

DR. CASSELL: Yeah, I wanted to read another way of saying it.

DR. SHAPIRO: All right.

DR. CASSELL: For research protocols that present greater than minimal risk, investigators must employ an independent qualified professional to assess the potential subject's capacity to consent. An IRB should permit an investigator to forgo this procedure only if grounds exist for using less formal methods of capacity assessment.

DR. SHAPIRO: I don't know if I have the whole thing in my head. It

seems to me it 's saying the same thing and that 's fine. You 're saying it a lot better, so I 'm not objecting to the language, but it seems to me to say....

DR. CHILDRESS: It says the same thing.

DR. SHAPIRO: Jim, what 's your response?

DR. CHILDRESS: My response is I agree. I think it goes in the kinds of directions that are being proposed for modification.

DR. SHAPIRO: Tom?

DR. MURRAY: I think that shorter is better, and I think that 's a principle we should employ all through these recommendations. So that 's good. I think this is a small point, but you can 't just say "if grounds exist" because, having listened to any number of debates, you can always find something that gives you grounds for something, no matter how goofy it is...

DR. CASSELL: Explain what you mean by "grounds."

DR. MURRAY: Something with good reasons for doing it.

DR. COX: You know consensus conferences they include all of these things that you 're talking about, but it varies tremendously from institute to institute. So this is the equivalent of well-meaning people earmarking research funds toward specific diseases.

DR. LO: Okay. But right now they give out training grants, and then there are center grants. You know we have a number of them. And the way you make things happen, say in your next renewal, we want to see how you 're going to address issues of decisionmaking capacity, informed consent for people who have impairment. We want to see someplace in your training grant and in your center grant a section that deals with that; so that it 's not necessarily putting extra money into those center grants and training grants, it 's to make sure that you know, I mean right now they have all kinds of initiatives saying you have to integrate basic science teaching. You have to have cross-disciplinary teaching. And that 's a way to sort of change how people train the next generation. I would like to see this included as one of those priority areas: how they score it, how many points they give in the review can be up to each individual institution.

DR. SHAPIRO: Carol?

DR. GREIDER: I always worry whenever I disagree with David. But I'm going to agree with Bernie on this one, because I think that this is something that has happened, at least in the research ethics area of training grants being tied to substantive education of students in post-docs in research ethics. So I think this has been the one thing that has forced people to actually think about it.

DR. SHAPIRO: Well, again, this is like David said; I still like this notion. And I think, Carol, why don't you and Bernie try to develop some language for this? Because I think that the general point that Bernie has been grasping would be the NIH could consider this. We're not making budget allocations for training.

DR. COX: Exactly. And what I've heard Bernie say is something different than I heard him say before. I heard him not say that we want to earmark money for training grants in this area. What I heard him say is just that we want people who have grants in this area to basically pay more attention to it.

DR. SHAPIRO: I think it's important to ask them to do that.

DR. COX: So all I'm saying is that the only thing I was sensitive to was the sentiment I'm very much in favor for. If we start earmarking funds, that's what I'm very much against, because I think that it's going to backfire.

DR. SHAPIRO: I don't think any of us want to earmark funds, but we want people to start thinking about this carefully.

DR. COX: Absolutely. I agree with that.

DR. LO: And list examples of things that they might consider doing.

DR. SHAPIRO: Okay. So, Bernie, you, and Carol, and Diane.

DR. SCOTT-JONES: Could I recommend some shortening of the language there? In 19?

DR. SHAPIRO: Sure.

DR. SCOTT-JONES: Because methods for affecting decisionmaking capacity would be included under study of cognitive processes. And I think it would

simplify that recommendation simply to say the NIH has sponsored research to expand knowledge about cognitive processes and informed consent processes among persons who have decisional impairment get some of the repetition of those phrases out.

DR. CHILDRESS: We have Eric's proposal on that, too, so we have formulations for this.

DR. SHAPIRO: Let's now try to reiterate this. I think that's an interesting suggestion. Let me suggest that you and Eric work on this language. So when we break in a few moments, we'll have a chance to get this together. Those are helpful observations. Is there anything else on 19?

DR. MESLIN: To just confirm that we're going to have a new recommendation.

DR. SHAPIRO: Yes, we will then have what was I think 4(b), which we decided separately will now become Recommendation 20. I don't think we need to discuss it any further, but that will now become a new Recommendation 20. We do have to also come back in a moment to make a decision on the involvement of family and so on, so we'll have to see where that comes. But now let's look at Recommendation 20 in the report itself, which may end up being some other number, of course.

DR. CHILDRESS: I had no proposals for change.

DR. COX: Yes, I have one proposal and it's to shorten it, okay? So make a period right after on line 13 right after "funds available," and delete "either as a new category of direct costs or through reimbursement of indirect costs." Again in my view, that's micromanaging. We want the funds. Okay. They figure out how to do it.

DR. SHAPIRO: Let me ask a question about that. I have no problem putting the period there. There is a big advantage any time anybody mentions shorter, so they jump to this. I think this is a good suggestion. This is an administrative issue that we shouldn't be dealing with. That's fine. I had the feeling when we were discussing this that I was always a little uncomfortable making this solely the responsibility of Federal agencies. And so the parenthetical expression "research sponsors, whether Federal or otherwise," I have always read in my mind this was one I want to touch base with the Commission on that this includes, for example, a university that might be the home of

this research. They are also a sponsor, because they are providing the sources for this. So I just want to make sure that I'm not misreading the intention. It's not because we're asking both the Federal Government its authorization to provide some support and the institutions that are involved, whether it's a firm, or it's a university, also to consider additional support. So I take it I haven't misread this.

DR. COX: Okay. Harold, that was exactly the underlying motivation of why I wanted to shorten this. Because if you start to designate, then you get into the battle of whose responsibility is it and with what funds, and that to put the emphasis on Federal and other okay? rather than on direct versus indirect. That's exactly my major motivation.

DR. SHAPIRO: So I know how to respond to questions. Any other comments here? Larry?

DR. MIKE: Well, then we should add not just research sponsors, but research institutions. Research sponsors to me connotes that people will fund the research, and that's usually the grantor. So if you want to make it more encompassing, I'd also add research institutions.

DR. MURRAY: On that point, I like the sponsor language. I think it should be internal sponsorship a university sponsors it through one of their internal research programs. They ought to fund. If it's NIMH that sponsors it, they ought to fund.

DR. MIKE: Spoken like a research institution.

DR. SHAPIRO: Let me just try some little tiny language change here and see if that offends enough people so we'll stick with what's already here. It would go that I'd like to put something like "all research sponsors." And then rather than have this parenthetical expression, something like including another parenthetical expression to replace this one. I haven't got the language unfortunately, it's escaping me but including, you know, the home institutions. I haven't got it right. I think I agree with Tom in principle, but I think that most people reading this will think only of the Federal Government, or only of the corporation that gave them the grant to test something, and so on. So let me suggest that I'll let me try to think of some language here. If I can't

come up with something better, I'll bring it back.

DR. MIIKE: Just an initial thing. I guess what we're also saying here, which is not stated explicitly here, is that what we are recommending should be just part of the cost of doing research. But I don't think it quite gets that in this statement.

DR. SHAPIRO: All right. Let me try to work a little language change here, but I think we all agree with the substance. All right. Jim, do you have anything further or any other recommendations?

DR. CHILDRESS: No. We have a version of 19, but also have to work with the work that Eric and Diane are doing.

DR. MESLIN: This is from Bernie and Carol, to replace the existing Recommendation 19: "The NIH should ensure that proposals for training grants and center grants include appropriate provisions for training and technical or other assistance on the issues discussed in this report, where appropriate. The NIH" and this also says, "and OPRR would consider using consensus development conferences or workshops to enhance discussion of these issues."

DR. CASSELL: And that goes on just in the next paragraph. Yeah.

DR. MESLIN: So that there can be two parts of Recommendation 19, which includes the general descriptions of the types of research that ought to be funded. This could be a second paragraph in the old recommendation that specifically suggests how NIH could engage further in this activity.

DR. MURRAY: So it includes most of what's there now in 19?

DR. MESLIN: It would include all of the current 19 modified by Cassell and Scott-Jones, and this would be the second bolded paragraph of 19.

DR. SHAPIRO: Okay. If we could go back now to the recommendation numbered I have forgotten. Was it 15, dealing with the families?

DR. MESLIN: Yes.

DR. CHILDRESS: And speaking on behalf of making this a matter of guidance, it seems to me an appropriate place for it would be on page 156. And the

reason for calling attention to context actually, we haven't included some pretty strong things, things that were really emphasized along the way, for example independent health care professional advisors is to put it under guidance. And it seems to me that a good place to include what we have in number 15 would be precisely on line 12 on page 156, as a new subheading. Because what we've just dealt with under independent health care and professional advisors would be the role, in the last sentence, of investigators making available information. It seems to me that this leads well into a discussion also of investigators involving the family, and I would much prefer to see it as guidance. What we've done under most of our recommendations would require our IRBs to consider how investigators were doing it. We tried to think about this one, and that language I think was in pretty quickly. What we're really talking about here is some kind of ideal we'd like to affirm, but not something we really want to put strong emphasis on in order to make it a recommendation.

MS. FLYNN: Let me just state my position.

DR. SHAPIRO: Laurie?

MS. FLYNN: My position I think I've made clear. But we seem to feel okay about raising it up to the level of Recommendation 18, which basically says professional organizations ought to develop materials. But something about researchers ought to engage caregiving families. Well, that's sort of just guidance. It seems to me that in the scheme of things the second one is much more likely to result in where we're going than calling on folks to develop materials. So again, if we're using some criteria of what we think is going to change the landscape for the better, I think not to have anything in these recommendations that specifically spells out the role of family is a mistake.

DR. SHAPIRO: Before we we're just going to have to again vote on this to decide which way we want to come down, either as a specific recommendation or highlighted in the guidance section in some way. But is someone working on language for this one?

DR. MESLIN: Yes, we have it here; Rhetaugh was. Shall I read it?

DR. SHAPIRO: Yes.

DR. MESLIN: "Investigators and others engaged in research involving as subjects persons with mental disorders should find ways to maintain contact with the family or friends who are actively involved in the care of the incapacitated subjects," is the language here, "and to keep them informed as appropriate."

DR. SHAPIRO: Let ' s just stick with this language before we get to deciding whether it ' s in guidance or somewhere else.

DR. BRITO: I like the changes, first of all. But when I separate that from recommendation facts to guidance, why not just shift "maintain" ? Why did we put it "find ways" ?

DR. CASSELL: Right to make changes.

DR. BRITO: To make changes? I think it makes it stronger. It just feels more like a recommendation, instead of just....

DR. SHAPIRO: Could you please read it again?

DR. MESLIN: Yes. "Investigators and others engaged in research involving as subjects, persons with mental disorders should maintain contact with the family or friends who are actively involved in the care of the incapacitated subjects, and to keep them, family or friends, informed as appropriate."

DR. SHAPIRO: I have a concern about the language. Let me try to express it. It ' s that we talk in the same recommendation about first of all, we use the word "patients" again.

DR. MESLIN: "Incapacitated."

DR. SHAPIRO: No, no, right at the beginning.

DR. MESLIN: "Investigators and others engaged in research involving as subjects persons with."

DR. SHAPIRO: My objection is, or concern is, we talk first of all about subjects of mental disorders, one category of people. But the second, the last sentence deals with incapacitated subjects. They aren ' t the same. They aren ' t the same population. This has gone to great efforts to try to can we somehow deal with this

language? Let me ask the question, first of all. Because people who maybe, Jim. I don't know who's the right person to ask this to is. Is this meant to focus on this interaction for all subjects with mental disorders?

DR. CHILDRESS: I don't know. I haven't been involved with this particular one.

DR. SHAPIRO: All right. Well, let's decide that then. How do you feel about that, Laurie?

MS. FLYNN: I think the concern here is for those who are most vulnerable, those who are incapacitated or potentially incapacitated, in the research study. I don't think we're asking beyond the research context, and I don't think we're asking beyond situations where incapacity is a risk.

DR. SHAPIRO: So as you see it, this is asking for this particular type of involvement for the most vulnerable, and maybe those with mental disorders who have become incapacitated for whatever reason. Is that I don't want to put words in your mouth. I'm just trying to understand what you said.

MS. FLYNN: Those who may be incapacitated or who may be at risk based upon the study.

DR. SHAPIRO: All I'm concerned about I'm perfectly happy to go with the broader view, not just incapacitated, but the broader population. If both parts let me explain the problem.

MS. FLYNN: Okay.

DR. SHAPIRO: If we go with the total population, people with mental disorders, you then have people, many people in there who are perfectly capable of making decisions.

MS. FLYNN: Right.

DR. SHAPIRO: And therefore there is no reason why we should impose some kind of family involvement, which they may or may not wish to have. Have I said something that you object to there?

MS. FLYNN: No.

DR. SHAPIRO: Okay. So do you view this recommendation and/or guidance as something to deal with the population of the mental disorders that are somehow no longer fully capable?

MS. FLYNN: I'm thinking I tend to think in terms of cases. I'm thinking about the case that brought all of the difficulty forward at UCLA. That case pointed out a larger problem: individuals participating in research becoming incapacitated, becoming, in fact, quite deteriorated, and the family dealing with this having no way to get information that would enable them to understand what was going on. And, ultimately, it resulted in....

DR. SHAPIRO: So this is a population who have become incapacitated or is losing their capacity in some way?

MS. FLYNN: Right, right. And, again, I'm talking about actively involved families.

DR. SHAPIRO: That's right. That's in the recommendation. Alta?

PROF. CHARO: First, I have to say I support Laurie on her instinct that this should be a recommendation rather than a guidance, because I think that it needs to be highlighted, if nothing else. And I see no harm in making the recommendation. I also wonder if something like the following might simplify and cover what we're trying to get at: "Investigators should involve caregivers in research for subjects who have impaired decisionmaking capacity consistent with rules governing medical confidentiality." I gather your focus is really on caregivers.

MS. FLYNN: Yes.

PROF. CHARO: More than anything else?

MS. FLYNN: Yes.

DR. CHILDRESS: With that change, I'd be glad to support it as a recommendation.

PROF. BACKLAR: I would too, but I would like to tie it to the legally

authorized representative, who I'm hoping is one of these people, so it should be "or LAR."

DR. GREIDER: Can you say "or"?

PROF. CHARO: I don't see any reason why we can't. But I mean the LAR obviously is involved already: the LAR is making decisions.

DR. MURRAY: What if we said "caregivers including LAR"? Laurie earlier objected to my wanting to tie it exclusively to LARs. Would that be appropriate, Laurie?

MS. FLYNN: Yes.

DR. SHAPIRO: I don't think it's inappropriate. I think it's a little redundant, but I don't feel strongly about it.

DR. MURRAY: So Laurie is going to make a point that sometimes in certain research protocols there may not be LARs.

DR. SHAPIRO: Do you want to repeat the language, Alta?

PROF. CHARO: Right. Here is what I have, and I'm not sure exactly where the LAR goes. "Investigators should involve caregivers in research with subjects who have impaired decisionmaking consistent with rules governing medical confidentiality."

DR. MURRAY: Could you do it again, a little slower?

PROF. CHARO: That *was* slow by New York standards. "Investigators should involve caregivers in research with subjects who have impaired decisionmaking consistent with rules governing medical confidentiality."

DR. CASSELL: Ooh, I like that.

DR. MURRAY: Eric noted he was typing by Canadian standards.

DR. SHAPIRO: Well, that's okay; I mean I think I agree with the general thrust of this, but I think I want to look at this language more carefully. Because as I at least I'm only listening. I haven't seen it in front of me. It's not you know,

what kind of involvement do you have in mind? A communication with caregiving communication I understand. Involvement of other kinds I probably can understand, too. But it's a different status, and that's what next step they should take in their protocol or something something different than that, but something. So I just want to be careful with the language here. Yes?

DR. SCOTT-JONES: My concern is a very similar one. And that is, what would it mean in a practical sense? Would it mean that that person might want to know what kind of condition in the experiment the person is going to be in? I'm just not sure what it would mean for a researcher trying to get the study done; what would the involvement be? I think in principle it's a wonderful idea. But I think if it's not more specific it's just too open to a variety of interpretation.

MS. FLYNN: I didn't want to make it complicated. But it's information and communication about the research. In the cases that we've heard about, the family caregivers didn't know that the person had been taken off of their medication. They couldn't get anybody to answer when they said, "What's going on now in the research? Why are we seeing these problems?" They couldn't get anyone to give them even basic information. They aren't privy to the protocol. They're not informed and involved in the research world. They've just got a problem there, and they're trying to do their best job with it. And they don't know what's happening.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I think that what Laurie has just said is very important. And I think it raises a problem that perhaps we're glossing over and maybe we should consider. One of Laurie's examples was, you know, a family member who doesn't know that the person is going to be taken off medication, so they don't know what to expect. Well, the researcher is not revealing that to the participant. So it seems to me that here is where there is one of those fundamental conflicts between research and clinical practice. Is that person going to want to know if we put this recommendation forward is a family member going to expect to know, and want to know details about the research that are not ordinarily given to the research participant?

MS. FLYNN: The research participant would know should know what the basic stages of the research are going to be. It would have to be laid out.

DR. SHAPIRO: Okay. Let me make an executive decision here on this after I hear from Trish.

PROF. BACKLAR: Two words: Did we say "actively involved" in terms of this?

DR. SHAPIRO: Yes.

PROF. BACKLAR: Okay. The other thing is that what we're really talking about is the welfare of that particular individual. And I think that that really is very is exactly what you're talking about. You may not need to know the specifics, but you need to know: is that person now at greater risk?

MS. FLYNN: Right.

PROF. BACKLAR: If this person comes home for the weekend and they start to do things that are peculiar, or at risk to themselves or others, can I have this information? It's important if I'm the caregiver that's very involved. So the welfare of the subject is what we are talking about.

MS. FLYNN: Right. That's what I'm interested in. I'm not interested in....

DR. SHAPIRO: My own view here, my own opinion on whether there should be guidance or a recommendation really depends on the nature of the language that we really end up with. I'm quite happy to highlight it in some way, and I'm sort of inclined toward putting in the recommendation. But if it gets really quite specific and seems constraining in some way, then I have reservations about putting it in a recommendation. I would just put it in as guidance, so people would have flexibility in interpreting it, and we would have made the point that we want to make that this is an important group. It needs more consideration than it's gotten in the past. And so on this one I feel that we really have to sell the language. I have other proposed language here. Let me just try it out, which I which Alta has just passed over. It says, "For research involving persons with impaired decisionmaking," which I think is the right way to get started, because we want to get a subpopulation here, not the entire population. "The investigator should discuss the protocol with effective caregivers consistent with rules governing medical...."

PROF. CHARO: Confidentiality.

DR. SHAPIRO: Confidentiality here. Now, this particular wording, which you know deals with it only at the beginning of things, right? It does not deal with ongoing discussions, which I think at least was a sense in some of the conversations we had before that there should be ongoing communication, as appropriate, with caregivers. So in my view it would need to be altered to include some appropriate ongoing communication as appropriate would change a lot, depending on the nature of the study, what the design was, and so on. Does that begin to get to something that 's sensible?

DR. BRITO: If we 're going straight to the subpopulation of persons with impaired decisionmaking capacity, did we not agree before about what the public testimony, and just in general, that not that we agree. It 's just that it 's a fact that people who have mental disorders are not always, or do not always have impaired decisionmaking capacity.

PROF. BACKLAR: Right, right, right.

DR. BRITO: So if we 're talking about your concern about the UCLA or the University of Maryland 's study to raise a lot of controversy, at the time that those studies began those persons did not have impaired decisionmaking capacity.

MS. FLYNN: That 's right.

DR. BRITO: So therefore, if we consider just the subpopulation, they would not be included in this. So we 're back to square one. We 're back to what I understood the problem was really with informed consent, and not government regulations. So now I 'm a little more clear about when it is that involving other family members is actually going to help. Because you already have the LAR is involved. You already have the protections for subjects with greater than minimal risk, and that 's what we 're really talking about here: washout studies, etc. And then if you include this addition of the subpopulation, just the impaired decisionmaking ones, then you exclude them. So I 'm not sure what added protection this would give as a recommendation.

DR. SHAPIRO: Well, I think the added protection here at least the way I see it is that it incorporates an important group of caregivers in ways ideally, in ways

that really would improve their overall welfare. Because these caregivers will see things that are not easily seen by the research team.

MS. FLYNN: Right.

DR. SHAPIRO: They will know things that are not easily known by those doing the research. And therefore that can serve, I think, as additional protection. I'm struggling with language here, because I don't have the language.

DR. BRITO: I guess I have to see the language. What I'm concerned with here is that I find if a person already showed that he or she has the capacity whether or not he or she has a mental disorder then why do they need the extra....

DR. SHAPIRO: They don't. They don't need this if they have a capacity of consent. That's where it starts off for researchers.

DR. BRITO: Okay. So my point here is that it's really not even held to be the most controversial study then as far as this point.

PROF. BACKLAR: That's true.

DR. SHAPIRO: But it still would be very important.

DR. BRITO: No, I'm not saying it's not important. I'm just saying....

PROF. BACKLAR: Well, except that you we are dealing with people. We are dealing, or I thought this report was about people who had fluctuating prospective incapacities. And this is because we're dealing with people in this particular population. Just because you say people can consent to a protocol, and many of these people will be able to, I mean that's the way we have structured it in a way. You still have to have these safeguards in place, because they may, during the duration of the protocol, boost their capacity.

DR. SHAPIRO: All right. The promised executive decision is as follows: if we can develop satisfactory language, it will go in as a recommendation. If we are really still at sea with language, it will go in as guidance. If we can't resolve that it will go in that way, and people will use it as guidance.

PROF. BACKLAR: So let's write this.

DR. SHAPIRO: And so we'll work on some language. Let me that is, as I see it, with the exception of getting this last item straightened out, presuming that the redrafting is along the lines that we have just talked about, and I have no reason to believe that it won't be, we are really through with our key recommendations not with our key recommendations, but all of our recommendations. And I will proceed accordingly.

Obviously, I want to repeat a couple of things here. One, I want to encourage, and any of you who have any concerns about any part of the report that we have not discussed, which is all of the text please, if you communicate with us we can respond in ways I think you will find reasonable and fair. Given the fact that we agree with everything, we don't have the same each of us has their own vocabulary which is somewhat different, so we have to be somewhat tolerant in that respect. But I think we can respond very effectively in most cases. So we will try late this afternoon to have some cleaned-up language so we can go over it one more time. But I think there we're talking about editorial changes. We're not talking about going back and changing anything further from this point or in any substantive way. We may find logical errors, of course. We don't want to be caught with a logical error. I don't think we're going to find that, however, at this stage, so that I will consider these recommendations as having been adopted pending we'll approve. We'll see the final language later on today, I hope. I don't think we have time this morning.

I want to extend an apology to everyone who has signed up for public testimony, since we really have not that was supposed to occur at 11:30, and we were just unable to get to it, and I apologize for the extra efforts and time that these people have to devote in order to give their public testimony. If any of the people who have signed up for public testimony are unable to wait until this afternoon, I hope that they will submit it in written form. We will look at it and distribute it to the entire Commission immediately. And I just apologize for that inconvenience.

With respect to our agenda going forward, we are going to have a very short lunch break. I don't know what that means here, but I don't know what's available in this area. But it's going to be very short, because I want to get back here pretty close to 1 o'clock, which is 35 minutes from now. Because we have there are people who are participating by telephone, and we have to move on to the letter that I

received from the President and begin our discussions of that area, so that if we get started at 1:15 or so we can help we have someone who is going to speak to us by telephone, who we're briefing at 1:30. But we'll need some minutes to get ourselves mobilized before that. So maybe it's more realistic to tell you we'll reassemble here at 1:15. We'll have to do public comments later on this afternoon, I'm afraid. So thank you all very much for your attention, and thank all of the commissioners for their work and attention to this report.

### **PRESIDENT CLINTON'S REQUEST RE: EMBRYONIC STEM CELLS**

DR. SHAPIRO: We are now in that part of our session where we are dealing, in at least a very initial fashion, with requests from President Clinton, which I read to all of you this morning. To reread just a part directly from the letter: "This week's report of the creation of an embryonic stem cell that is part human and part cow raises the most serious of ethical, medical and legal concerns. I am deeply troubled by this news of experiments involving the mingling of human and nonhuman species. I am, therefore, requesting that the National Bioethics Advisory Commission consider the implications of such research at your meeting next week and to report back to me as soon as possible." This is a paragraph from the more complete letter, which I read this morning. But that's the part of it which we're addressing now. The second part of the request we will address over time.

I have asked Dr. Brinster of the University of Pennsylvania to respond to any questions that we might have regarding any aspect of the science that is related to this and the nature of the experiments. He will at least answer to the best of his ability any questions that we have. And then, of course, we can see where that discussion leads us. And then, we, of course, will have our own discussions subsequent to that. And as I said, we'll do this in a Q&A format. This is what Brinster proposes at the first. So let me turn to Eric, first of all, to pose the first few questions that we have, and then we'll turn to the commissioners to see what questions they have. I would ask the commissioners if they have a question to please identify themselves so that Dr. Brinster will also know who it is that's asking the question. Let me then turn to Eric Meslin. And

let me just ask Dr. Brinster if he can hear us.

DR. BRINSTER: It 's very difficult, but I can hear you.

DR. SHAPIRO: We 'll do the best we can. Let me ask everyone to talk as directly as they can into their microphone.

DR. MESLIN: Good afternoon, Dr. Brinster. It 's Eric Meslin. We spoke yesterday on the phone, and thank you very much for being available by teleconference today. There have been a number of questions that have been put together that we hope you will be able to respond to. The first is: What is the state of the art, to the extent it is known, regarding production, including isolation and culture, of human stem cells?

DR. BRINSTER: Well, the recent publication I think the state now of human embryonic stem cell research, what was published in *Science* last weekend, will probably appear in the next national proceedings of the National Academy of Sciences. And in one case, apparently certainly pluripotent embryonic stem cells of human origin were produced from embryo outposts. And in the second report, by Gerhardt, it 's likely that similar cells were produced from fetal germ cells. These are two well-established techniques in mouse embryology and the generation of these pluripotent and totipotent, in fact, stem cells. So that much we know from the published reports: that many tissues can develop from the stem cells. The final proof of totipotency is not likely to be achieved, because the final proof is the generation of germ cells in another animal that arises in part from stem cells but they certainly are widely pluripotent now. Does that answer your question?

DR. MESLIN: I think we will allow the statements to stay, and if commissioners wish to jot down their questions back for Dr. Brinster, we 'll continue on. The next question: How are nonhuman cells used if the desired product is a human stem cell?

DR. BRINSTER: All right. Can you repeat the question? I 'm not sure I understood it.

DR. MESLIN: There are two versions. I 'll read you this version. The first is: How are nonhuman cells used if the desired product is a human stem cell?

DR. BRINSTER: I couldn 't hear the connector. How are stem cells

used?

DR. MESLIN: Let me rephrase it in a different way.

DR. BRINSTER: Thank you.

DR. MESLIN: Or why, would be another version. What research has been done that would help determine if a nonhuman oocyte might be used to produce a human stem cell?

DR. BRINSTER: Oh, okay. Published research is not very direct. It's been known for many years that oocytes in general reprogram nuclei in a number of species, including the mouse. That technique was used to generate the clone animals, and to demonstrate that complete repro does occur. I'm not aware that any published information has appeared showing that other species will reproduce from another oocyte. There is the *New York Times* report that is a narrative description of what was done, but not published.

DR. MESLIN: Could you say something about whether we know if the resulting product is totipotent or only pluripotent?

DR. BRINSTER: I don't even know if there is. I know that there is a claim that someone has put a foreign nucleus in and made stem cells in a cow oocyte, but that has not been published, or, in the second instance, that's required in Science that it be repeated by someone. So, there is no proof positive that this had taken place that I'm aware of.

DR. MESLIN: As a more general matter, though, could you help us understand the difference between totipotency and pluripotency?

DR. BRINSTER: Well, the easiest way I think of probably four levels of potency or ability in a cell, and the first one is totipotent. That's the ability to make any cell, including germ cells, and the last critical part, including stem cells. Pluripotent cells are the next level, and this level can produce more than one type of motor cell. It may produce many types, including everything but one type, and that one type is generally the germ cell, which is the most difficult to regenerate in those terms. So the pluripotent cells may make only blood cells, or it may make only sperm cells, or it may make only skin cells, or only intestinal cells, but it makes several types in most cases, so it's plural.

Multiprogramming is another term. The third level of cell, differentiating cells, becoming some particular type of cell, either growing from one mouse cell. Their fate is generally determined, but they have changing characteristics. And the fourth type, a fully differentiated cell that will change no more, like on the surface of the skin or the final cell on the intestinal epithelium or a nerve cell. And the type that you're interested in today is totipotent and pluripotent. And the difference is the totipotent will make germ cells, and make every cell; the pluripotent makes many cells, but cannot make every cell.

DR. MESLIN: Is there uniform agreement or consensus within the scientific community, be it in the animal research community as well as the human research community, with the use of those terms? Is there any confusion or ambiguity that you think is existing?

DR. BRINSTER: I don't think there is very much ambiguity, especially between totipotent and pluri. Some people call pluripotent, multipotent. And in some of the old literature people use pluripotent and multipotent without knowing whether they could make every cell.

DR. MESLIN: Could you say something about the resulting product, that is to say, the product that we've been discussing here this afternoon that you've just referred to, that was reported just recently, if the cell as an organism is a true chimera or not?

DR. BRINSTER: Repeat the question, please.

DR. MESLIN: Would the resulting product, the cell or organism itself, be a true chimera?

DR. BRINSTER: Well, the word "chimera" has many definitions, too, depending on the background and who's using it, in Greek mythology it's one thing, and in biology another. But in terms of the question, are you referring to the reported paper about putting a human nucleus in a bovine oocyte?

DR. MESLIN: Yes.

DR. BRINSTER: That would be considered a chimera by scientists?

DR. MESLIN: Yes.

DR. BRINSTER: I think most scientists would probably not regard it as a chimera because I think most scientists think in terms of the old Greek definition of a chimera, or the more recent biologic definition, where there is a mixture of cells in the body. I don't think, for example, that people regard transgenic animals as chimera, where there is an actual mixing of genes of several species, one or two genes of one species put into a mouse, for example. I don't believe I have ever heard anyone call that a chimeric animal. So I don't think such an animal, that if an animal were generated from an oocyte, say of a mouse, and the nucleus of a dog, would be considered a chimera.

DR. MESLIN: Just so we're clear: what would you refer to it as?

DR. BRINSTER: I think it would be a dog, because I think no one knows what's going to happen, or if it, in fact, has been achieved. But if it did happen, it's likely that the nucleus would it seems probable, one possible outcome, that the nucleus of the species transplanted into the oocyte would actually multiply would change the proteins, and the proteins would become, for example, the proteins of a dog, if you were in a mouse oocyte. And it's likely that mitochondria would be transplanted with the nucleus, and it would be very difficult to transplant nuclei, I think, without mitochondria. Those nuclei might be placed in the nuclei of a mouse oocyte.

DR. MESLIN: Thank you very much. Those are sort of the initial kickoff questions to get the Commission oriented. Now I'll let Dr. Shapiro....

DR. BRINSTER: Well, the committee should realize that the mitochondria the proteins that make the mitochondria are coded by genes in the mitochondria, but also by genes in the nucleus. So it's likely, then, that there has to be a match between those two in order for the mitochondria to survive, that some mito must be made that can survive in order for the cell to survive. Is that clear?

DR. SHAPIRO: Yes. This is Dr. Shapiro. I have one question, but let me turn first to the other commissioners to see if they would have some questions for you. Professor Charo?

PROF. CHARO: Hi, this is Dr. Charo, and let me just tell you I'm from the University of Wisconsin with a background in law rather than science. Dr. Brinster, I

wonder if you 'd answer two questions. First, assuming you have fused a human differentiated somatic cell with a cow oocyte, does this fused cell have the ability to divide in an organized fashion through embryonic and fetal stages such that it could become a baby?

DR. BRINSTER: I think the question was if you fused a human nucleus to a bovine oocyte, would it be able to develop fully.

PROF. CHARO: Correct.

DR. BRINSTER: I can 't answer that, and I don 't think we have any published information to answer that. It 's possible that it could. But it 's also possible that it would die, that other things that are unknown make it work.

PROF. CHARO: Second question: Would such a fused cell divide initially in a way that is virtually identical to that of a normal human embryo so that it could in theory be used as a substitute for normal human embryos for the purposes of early embryo research?

DR. BRINSTER: I think that 's possible, but not yet proven that it will occur. I think that 's possible, but it hasn 't been done yet as far as I 'm concerned.

PROF. CHARO: Thank you.

DR. SHAPIRO: Thank you. Other questions from members of the commission? Yes: Larry Miike.

DR. MIIKE: This is Larry Miike. I 'm a public health person. Given the various scenarios about creating tissues and organs, etc., what 's the state of the environment in which such cells would have to be nurtured in, for example, making a skin cell versus making a whole organ such as a liver or a kidney?

DR. BRINSTER: It 's very difficult to hear the question. I don 't know if the pickup is bad. I can hear parts of it, but I couldn 't hear the whole thing.

DR. MIIKE: I guess, to make it simple, what 's the state of technology in the environment in which the cells would have to be nurtured between making cells versus making organized organs?

DR. BRINSTER: Okay. I think I understand: the question is what's the state of the technology to convert a stem cell into an organ. Is that correct?

DR. MIKE: That's right.

DR. BRINSTER: I wonder if there's a microphone down there that each person could use, because it's difficult for the questions. But I think I have that question correct, and I would say that the technology is under development and has been for a long time regarding mouse embryonic stem cells. The work on mouse embryonic stem cells goes back more than 25 years that people have been trying to understand development from these and direct them to specific tissues. Now certainly the pace has increased in the last five or 10 years, and so some cells can now be directed toward muscle and perhaps to the hematopoietic system to make blood precursors. So that in a couple of instances where a couple of tissue cells can be made, in other words converted from a pluripotent cell with wide capacity that is a stem cell, known as an embryonic stem cell to a stem cell for the blood system or for a muscle cell. And in those cases it's been shown that they will participate in the normal system of a mouse. No organ, to my knowledge, has been made. And that would be a very complicated technology to evolve.

DR. SHAPIRO: Thank you. Tom Murray?

DR. MURRY: Good afternoon. Let me first establish that you can hear me.

DR. BRINSTER: I couldn't hear that.

[Laughter]

DR. MURRAY: Good! You answered my question! Let me try again. Can you hear me, Dr. Brinster?

DR. BRINSTER: Yes. I can hear you.

DR. MURRAY: This is Tom Murray from Case Western Reserve University. I have two questions. The first is what information, if any, do we have from studies with animals involving use of oocytes from one species and the nucleus from another to tell us whether those organisms are viable and what sort of identity they would have should they be viable. That is, what species would they be if they were

viable?

DR. BRINSTER: Well, the answer to the last question, I don't know; if they were viable there is, I think, no doubt they would be the species of the nucleus, because the cell would be programmed to become compatible with the nucleus. The cell would not be the cell cytoplasm would not be able to change the species of the nucleus. All of the coding information is in the nucleus. And in regard to what information we have, I have to say that there's no new information of which I'm aware that shows this can be done. There's old information where you can show that the nucleus of one species is changed when you put it into another species, but as far as I know there's no published report indicating you can generate an early developmental stage such as a blastocyst that is, three or four days' development by using the nucleus of one species and the cytoplasm of another species. There are rumors in the scientific community that people are trying it. But I have not seen anything publicly, and in science that has to be the first step.

DR. MURRAY: Thank you for that answer. Let me try one additional question.

DR. BRINSTER: Okay.

DR. MURRAY: Do you see any compellingly important scientific research that could be done by the use of, say, a bovine embryo and a human nucleus, that could not be done by using embryos, by using, rather, oocytes and nuclei from other species, but not involving either human oocytes or nuclei?

DR. BRINSTER: I'm not sure...was the question, is there any advantage to using oocytes, nuclei of humans rather than the nuclei of other species in the bovine? Is that the question?

DR. MURRAY: Right. Is there any compellingly interesting science that could be done at this point that would require us only to use human DNA rather than, say, DNA from another mammal?

DR. BRINSTER: I think that initial experiments can be done in laboratory animals or farm animal species to show the feasibility of this approach and also to work out details of how it can be done and what would result if it works. As I

said, I think there ' s a little doubt if it will work, that what will result is an animal of the nuclear species. But I think that if you want to use it in humans and also on other primates as models for human disease, that you have to eventually do experiments in nonhuman primates and with human cell nuclei. And aside from the basic science research and understanding of developing programming for the structuring of tissues, one of the great values of this embryonic stem cell technology is the potential to make some tissues for replacement in human disease.

DR. SHAPIRO: Thank you. Carol Greider?

DR. GREIDER: Hello. This is Carol Greider from Johns Hopkins University. I ' m a molecular biologist.

DR. BRINSTER: Yes.

DR. GREIDER: I have two questions. The first is how many cell divisions do human cells go through before the zygotic genome would take over?

DR. BRINSTER: That ' s difficult to say because those types of studies haven ' t been done in the human. But as a general principle, the mammalian genome begins to express a few genes almost immediately after fertilization. Certainly by the two-cell stage the mouse embryo is expressing genes. And then progressively more of the zygote genes are expressed as the embryo proceeds. But by the blastocyte stage I would certainly guess that in every species the embryonic genome is in control, probably beginning maybe at the eight-cell stage. The shift is pretty dramatic at the eight-cell stage in many factors of embryonic development. That ' s about two to three days after birth.

DR. GREIDER: Yes. Thank you. And then the second question relates somewhat to that and it has to do with the possibility, if one were talking about making, going through implantation and the possibility of immune rejection, what species ' antigens would you expect at the stage of implantation on a cross-species oocyte?

DR. BRINSTER: Well, I think that if you have put the nucleus of a dog sample into a mouse then you would have to transplant that oocyte back to the dog. It would not grow in the mouse, is my guess, because the species difference is too great. But if it went back into the dog, I would expect that it would be accepted, because we know that chimeras exposed to several strains of mice are not rejected in utero. The

immune system is polarized as the embryo develops. I guess that 's an appropriate term for the committee. Does that answer your question?

DR. GREIDER: Yes, thank you.

DR. SHAPIRO: Other questions? Excuse me. Professor Charo again.

PROF. CHARO: Dr. Brinster, could you please comment on the reported presentation by Neil Furst last January in Boston on his experiments using fusions of mammalian species not involving humans? Specifically the report his reported speculation that these fused cells would not in fact be viable after a period of days.

DR. BRINSTER: After he transplanted the nucleus into the oocyte?

PROF. CHARO: Correct.

DR. BRINSTER: Well, I think it 's like many things, and as I indicated in the beginning, these are only narrative reports in the newspaper. We do not know whether this system would work. And I assume that it will be published soon and that other groups will then try to report it, where groups that are reported to be working in this area will in fact actually publish rather than in a science journal. And then it can be repeated. So until that 's done, I think none of us really knows what would happen. It is possible that they would die after a few cleavage divisions. Most of the questions I 've responded to have implicitly assumed or wondered what would happen if in fact they did live. Whether they will live is unproven.

PROF. CHARO: One last question, if I may? For medical applications in the human, in the future, people have suggested that cloning one 's own tissue to generate stem cells for personal cell therapy would be important. Would you see the easy availability of bovine oocytes in which to, with which to clone one 's own cells as a viable way of pursuing this and avoid the need to obtain human eggs from live women?

DR. BRINSTER: Well, I think the interesting or potentially important aspect of the proposed procedure, where you transplant a nucleus into the oocyte, is that you could use the nucleus from the person or individual that needed the tissue and therefore circumvent the immunological problems that would arise just using a general embryonic stem cell of human origin. Because there will be immunological problems, just like with organ transplant. But if you take the individual 's own cells and put them into

an oocyte, I'm not sure that bovine oocyte is the oocyte of choice. It just happens to be the one that's reported. And so if you transplant it into another oocyte then you have the potential of making embryonic stem cells that would be compatible with that individual, which is a major improvement in technology and would not require immunosuppression. And to use those cells to replace bone marrow, or muscle cells, or whatever.

DR. SHAPIRO: Other questions from commissioners? Yes, Professor Scott-Jones?

DR. SCOTT-JONES: My name is Diane Scott-Jones. I'm a professor of psychology at Temple University. I'm a developmental psychologist. And my question is regarding the possible use of this scientific work. You've mentioned that one possible use is to cultivate tissues for the replacement of diseased tissues in humans. Is there any other possible scientific use of this work that you anticipate?

DR. BRINSTER: I think embryonic stem cells.... I assume you're talking just about the human embryonic stem cells?

DR. SCOTT-JONES: Yes.

DR. BRINSTER: Well, I think that probably most scientific questions regarding developing differentiation from stem cells and other tissues could be addressed in the classic way by using mostly primitive species or lower species, like the mouse, and then eventually looking at primate species. So I see probably the medical aspect here as extremely important. But there are also always the small differences between species in terms of regulation of tissue development, which you do not anticipate. So just as most experimentation can be done first in the mouse regarding the logical understanding of the immune system, and then into primates and so on, I think the same rules exist here, where most of the information is obtained as simply, with the most economical means, in lower forms, and then, eventually, some work has to be done with the human.

DR. SCOTT-JONES: I have one more question. We read that there's been an application for a patent for these cells. Do you have any opinion on the appropriateness of that?

DR. BRINSTER: No, I can't say that I have an opinion on it. I don't

know very much about law, and there are many people that know ethics better than I do, so I really have to say I don't have an opinion.

DR. SHAPIRO: Thank you. Professor Murray?

DR. MURRAY: Hi, it's Tom Murray again. You've said a few things about the fate of mitochondria, of the oocyte mitochondria, and what would happen. Do we have any really solid scientific data about the likely fate of those oocyte mitochondria, or is this mainly a kind of well-informed speculation about their likely fate? Is it possible, for example, that mitochondria in the receptive oocyte might take the same signals to divide and multiply and go with the daughter cells as the mitochondria from the nuclear species?

DR. BRINSTER: Yes, that is possible, but we don't know much information. It's been a topic of interest. In fact we tried very early, maybe 15 years ago, to transplant mitochondria, and several of my students have subsequently done experiments transplanting mitochondria to look at how long they last. At least one of these students was successful in showing that when you transplant mitochondria to the fertilized egg, they are still present in the blastocyte stage. But it's a very difficult experiment, and it's not clear how many are present. We know also that there is considerable similarity among, or conservation among, the proteins of mitochondria in related species. But we do not know the absolute answer to the question that you ask. For example, is the dog close enough to the cat, or is the human close enough to the cow, so that the genes, so that the number, so that the genes that are present in the nucleus will support the development and interact with the genes that are present in the mitochondria from two different species? For example, will the human nuclear mitochondrial genes provide proteins of sufficient similarity so that they will interact with mitochondrial gene proteins to construct hybrid mitochondria? We do not know the answer to that. That can be worked out to a great deal of perfection by using animal species, and it's, as with anything in biology, you really have to do the experiments to know the answer.

DR. SHAPIRO: Thank you. Professor Greider?

DR. GREIDER: Yes, this is Carol Greider once again. Following on the mitochondrial question, in the case where instead of transplantation one uses cell fusion

to fuse a somatic cell with an oocyte, one would presume that you would also have then a mixture of mitochondria. Might you then expect that the same species' mitochondria, that is the mitochondria that had the same species as the nucleus, would then win out in the competition? Or do you have any expectations in this scenario, where there's not transplantation?

DR. BRINSTER: When cells are fused both nuclei are present, though initially both types of mitochondria could be supported. I'm not aware of any studies; I can't remember exactly studies that determine whether one type of mitochondria is eliminated. It seems to me that they are, but I cannot vouch for that because it's not in my field, and I cannot recollect for certain. But it's a good question whether when you fuse two cells from two different species, like human and mouse, which is done many times, which mitochondria persist. That may be in the literature.

DR. SHAPIRO: Thank you.

DR. BRINSTER: But also it will be very complicated to determine, because quite frequently the chromosomal complement on these cells is abnormal, so that some chromosomes for both species are retained. And that is not the situation in which we're interested. I don't know that looking in the literature will answer the question that you really want, and that is whether any mitochondrial genes persist into the adult as a nuclear transplant into an oocyte.

DR. SHAPIRO: Thank you. Any further questions? If not, then Professor Brinster, let me once again thank you very much for your willingness to join us in this rather unusual way. I very much appreciate your patience, and thank you very, very much for your help.

DR. BRINSTER: You're welcome. Good luck in your meeting.

DR. SHAPIRO: Thank you.

DR. BRINSTER: Goodbye.

DR. SHAPIRO: Let me say a word about how we're going to proceed. We only really have, I hope we'll only use right now, about another half an hour to discuss further aspects of this. My intention is to appoint a bucket or something, with that old phrase that we used to use, to actually draft a letter back to the President this

evening, which we can approve or not, as the case may be, tomorrow morning. If we don't get that far, then we'll approve it by e-mail or something else like that in the next day or so. I do feel an obligation to get back sometime this week and as early as tomorrow, but that depends on just where our discussion takes us. So that's what I'm intending to do. All of you can wonder which of you is going to get appointed to this, but that will be a matter of mutual agreement. I'll do that at the break. But in any case, let's just open up the floor for discussion. I think the focus of discussion ought to be on what is the nature of the kind of response we can make. Given, obviously, there's a huge number of unanswered questions here, what could we do that would both be helpful in clarifying in an initial way some of the issues here? While obviously we're going to have to postpone other aspects of the issue until we can deal with this in greater depth. The thing that we absolutely don't want to do is answer beyond our capacity or knowledge at this stage. We can't do that, and I'm sure no one wants to do that. So let's just open it up for discussion and suggestions about how we might structure a response, what kind of things we might include, and so on. Tom?

DR. MURRAY: Well, we could certainly reemphasize something that we said in our report on the phone, that maybe that technology like this, and this does involve somatic cell nuclear transfer, it would be wrong to attempt to make a child from this technology. We can say that we believe this falls under the prohibition we recommended with respect to trying to create a child by cloning. That would be one that's not a response to all the issues raised by it, but it's just one thing we can reemphasize.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I would like to see us comment on the appropriateness of this kind of information appearing in a major newspaper before scientific articles are available for review and comment. It seems to me that this isn't the way we want science to proceed, that science is very cautious, that there's a high value placed on replication and on careful peer review. And I would like to see the letter and make some comment about the process of disseminating the information.

DR. SHAPIRO: Eric, then Bette.

DR. CASSELL: Well, the President expressed concern, and so did other

people reading it, about the danger of this phenomenon of the transplantation of two different species, including the human being. I would like to hear something from David and Carol about that danger, and if in fact there is a danger, what would have to happen before the danger is realized, and so forth, so that we directly respond to the first of the questions.

DR. SHAPIRO: I could just add on to that, and then maybe we can turn to see if either David or Carol can help us understand this better, and then we'll go to Bette's question. The President does refer to the mingling of human and nonhuman species, reacting not as a scientist, but it seems to me that in one way that's been going on for a long time that is introducing, as I understand it, human material into nonhuman animals in one way or another to do various things. Whereas I think that's not I don't know, but it didn't seem to be what the President quite had in mind. So as you try to respond to Eric's question, I just wanted to add another uncertainty to your question I have in my mind to that. So maybe, I don't know, David or Carol? Which one of you would like to have anything to say regarding Eric's question?

DR. COX: I'm happy to start. I really do think we start past the concept of mingling proteins, because that's what recombinant DNA is and we do that for a living, so we're past there, all of us are. So let's start by mingling cells. But that's been going on for a very long time, too since the 1960s. And it doesn't just happen experimentally with scientists, but it actually happens inside different organisms, too. But obviously not one cell from one organism, one cell from another organism. That happens only with scientists. Hamster cells were fused with human cells all the time. They create hybrid cells. And the knowledge about what happens when you do that, which cell takes over the answer is it's complicated. There aren't any really defined rules. But the point is that those are cells, and cells aren't organisms, all right? Cells are cells. Those cells don't turn into anything but cells. They don't turn into living, what we would call organisms, defined as organisms. So for me the question here, what to say to the President is, that there's nothing new here in the context that cells from different organisms are being used that's part of ongoing science, and it has been for 20 years. What's new is the concept that cells between organisms are fused and could turn into an organism, that is, a living being. And the answer to that is, nobody has any idea, because as Dr. Brinster said, we don't know. And based on what we know about fusing somatic

cells from different organisms, we really don't know, because there's not even any standard prediction that you can make from that. So to me, it's that this isn't if we knew for a fact that fusing, putting a human cell in a bovine oocyte, would not lead to anything past two-cell division. That is to me not a new issue, because you cannot make an organism that way.

I'm not saying there aren't ethical issues involved there. For me, the issue is whether you can make an organism or not. We do not know the answer to that. And so what do we do about that? That, to me, is the \$64,000 question. But it's not the idea, not the visceral response that everyone gets, including myself, when you talk about mixing a cow cell with a human cell. That's not where the action is. So those are my sort of differentiating points. And the difficulty is knowing whether you put that human nucleus into a cow or, as far as I'm concerned, you put any other species into any other species' oocyte, whether that can actually divide and make a living organism. We don't know the answer.

DR. CASSELL: May I follow up, just quickly?

DR. SHAPIRO: Yes, sir.

DR. CASSELL: Does that mean, David, that leaving out this, you know, this spectacular nature of the newspaper, and that if this was your line of work, you would use another species first? Not human-cow but whatever mouse-cow?

DR. COX: Yeah, but let's be really candid. Because of the differences between species, you will never know whether you put that human cell into another oocyte, whether it will lead into an organism or not. Okay? You may have some ideas about it, but you won't know.

DR. SHAPIRO: Carol?

DR. GREIDER: I agree with everything that David said. What is new here is not the issue of mixing cells but rather, what people are concerned about is, can this form an organism? And that's where the concern is, and that's back to where we were for the cloning report. If these are just cells, however, that's where the importance of the human comes in, because the second charge and the second part is going to be to look at the issue of human embryonic stem cells and what one can then do medically with

those differentiated cells from the pluripotent cells. And there are a lot of really exciting possible therapeutics that we pointed to, as a matter of fact, in the cloning report, that might be useful. And so that 's an answer as to why human because all of those medical possibilities you would have to have human cells for. And so I don 't think that those issues, which are sort of a secondary issue, that if we agree that we 're just working with cells then the issues become somewhat different, and I think we 're going to deal with those in a separate issue.

DR. SHAPIRO: Larry? Let 's see, Bette, I 'm sorry.

MS. KRAMER: That 's okay.

DR. SHAPIRO: Larry?

DR. MIKE: I guess I 'd look at it in a slightly different way. I think what we should concentrate on is a short report, because the second part of the letter really asks us to take a look at the broader issues a straightforward description of what these techniques are and what the attempt would accomplish. I would look at this and say, for example, on the human cloning issue toward a baby, is there any advantage to doing this over using human cells? For one thing. Doesn 't seem to be any unless you want to make thousands of you the same, I mean, you know, just an implausible scenario. And then, if we 're not dealing with that, I think because some of the issues we raised were that, if we were looking at our old cloning report, we were talking about dangers to women who have to be the source of the oocytes. That would not be present here. So I would look at what are the end results that we 're aiming for, and do they raise the same kinds of issues that we did in our original cloning report? And I think we should just let it lay that out on a very factual basis. And I think that this report, since we need to be short, really should be spending most of its time just sort of explaining what exactly we 're talking about, because the reports in the newspapers give a sense that it 's a really alarming situation, and maybe it 's not.

MR. STEVEN H. HOLTZMAN [on speaker phone]: Hello? Hello?

DR. MESLIN: Steve, is that you?

MR. HOLTZMAN: Yes, I can barely hear you.

DR. MESLIN: Very good. You 've joined us. Welcome. It 's Eric. We 'll

try to speak directly into the microphones. The pickup is not always easy. This is Steve Holtzman, as you know a member of the Commission who was unable to be here today, and I asked him to join us for this part of the conversation.

DR. SHAPIRO: Let me ask these questions are so simple I hesitate let me go to Bernie first. I'll save my questions. I'm sorry, Bernie.

DR. LO: Trying to follow up on the lines of thought that other people have started, it seems to me that we do have a framework, both from our cloning report and other previous reports, and I think the points that were made about how we don't really know what's going on because there's nothing published and the details aren't there, and the points David and Carol made that what's unique here is the possibility of having a totipotent, pluripotent or even totally potent cell that might be capable of developing into an organism makes it different than other types of protein or cell commingling. But if we think about two of the purposes to which these cells might be put, one would be implantation with development to a mature organism. And as Tom suggests, we probably want to say that raises a lot of grave concerns. In our cloning report, we sort of set out recent concerns about safety and concerns about ethics. It seems to me again, here, that general framework is useful. That from what I heard Dr. Brinster say, there are a lot of concerns about is this going to work, what's going to happen, and have we done enough, even taking into account David's point that eventually, if we're going to, if we want to use it for human stem cell transplantation, we're going to use human nuclei, should we be doing some preliminary work on other transspecies transfers into oocytes? Is it really premature to start thinking about either transplantation or certainly implantation until we've resolved some of these safety questions? Then, I guess, there are these sort of, I don't know what you want to call them, philosophical concerns, or just uncertainties, about what would it mean, assuming this worked and if it were safe, what would it mean to have an organism, or to have a cell that had the potential, perhaps if implanted, of developing into an organism that had the nuclear DNA of a human being and either the mitochondrial DNA of another species or, if you did a couple of transfers that was in the letter we talked about somehow you've got the human DNA in there as well. And we haven't even begun to think about what that would mean; isn't that the point of what David and Carol were saying? This is sort of a new conceptual lead, and maybe we want to say that we certainly need to start

to think out both the safety issues and the conceptual issues before we just say, "It's a green light, go ahead, it's no problem." But I think the framework we developed in terms of safety, scientific concerns, and then also sort of moral concerns is useful.

DR. SHAPIRO: David, then Jim.

DR. COX: Yeah, so you helped me a little bit Bernie, because now I'm just going to not consider for a moment the ethical considerations and simply consider some scientific considerations. So one of the things right now is that it's very difficult to get human oocytes from purely scientific points of view. And so to study issues about making pluripotent stem cells, irrespective of making babies, irrespective of ever talking about implanting it. As a scientist, one might think that it's easier to basically do the fusions between bovine oocytes and human cells. In fact, from a purely logistics point of view, that's probably correct. That's not even human subjects work, right? Because as we've already said, there are all kinds of fusions that go on right now between human cells and mosquitoes, okay? There have been fusions between human cells and carrots! Right? So that fusion between a bovine oocyte and a human somatic cell? Scientists wouldn't even bat an eyelash from a scientific point of view. Now I think that most of the public doesn't realize that these kinds of cell-cell fusions go on, so I just want to emphasize that. But I would say that as a scientist, if I wanted to understand these issues of reprogramming cells, which is what this is all about from a scientific point of view for many scientists, is that mixing things between species confounds the science tremendously. For the reasons that I said, that we can't predict who's going to win and in fact, okay, that each cell contributes different amounts of stuff, which makes it difficult to do controlled experiments. So I'll just say, this is what I do for a living. I make these kinds of hybrid cells, and it's been disappointing to me over the last 25 years that I haven't been able to learn more about what controls them. So as a scientist, in my area of expertise, I would not choose to do an interspecies experiment first. That doesn't mean that one couldn't learn something from that at a particular time, but that, I don't think, is the preferred way to do the experiment. So one could say, Bernie, from a purely scientific point of view, this is the best way to go. But I would argue against that. And that's irrespective of any of these other issues. But just to emphasize again that I would really like to make clear that fusing cells of different species is not new, and it's been going on for a very long time.

DR. SHAPIRO: Bernie, do you have another comment before we go on?

DR. LO: I just wanted to ask David to clarify his comments that it's not new to fuse the nucleus from a human cell and the cytoplasm of the oocyte from another species. My understanding is that ordinarily those experiments do not lead to a pluripotent or a totipotent cell. Now is that because the experiment wasn't designed that way, or that they failed? You sort of said what's new here is the potential to develop into an organism. So how can you explain to us how what's being proposed or talked about here is different from these experiments you've been talking about?

DR. COX: One of the ways that it's different is that an oocyte and this is also an extremely important point an oocyte isn't just another cell. An oocyte is a very special type of cell. In fact, without an oocyte, to my knowledge, you don't make an organism. Think about that. It's that there's no other somatic cell, okay, that you can do without except an oocyte. Ultimately, even if you have a blastocyst, we put a somatic cell in, that had to have an oocyte to start with. So the oocyte is an extremely special cell. As far as we know, that's what it takes to have an organism. You can't do it without an oocyte. So that's definitely different.

DR. LO: It's unique that they used an oocyte as the host?

DR. COX: Well, but I don't know that it's unique because other people have. It's not unique that they've used an oocyte, because there have been other experiments, as was reported in the human embryo report, where they basically fertilized hamster oocytes with human sperm. So this isn't the first time that somebody has put a human nucleus into an oocyte of a different organism. But I do think what's unique about it is the concept, and what people are struggling with from the ethical matter, not from the scientific point of view, is what would happen if that actually could develop into an organism? From a scientific point of view we don't know whether that could develop into an organism, even if it was able to divide once, twice, three times, we simply do not know. But I would just say that the pure science, not even talking about it turning into an organism, looking at other issues, that I believe is a start. It's not the preference from a scientific point of view to do the mixed species first.

DR. SHAPIRO: Thank you. I have a number of people on my list now, starting with Jim, then Dr. Charo, then Arturo. Jim, you wanted to comment?

DR. CHILDRESS: Just a matter of observation, given our experience on the cloning report. I just want to make sure that we don't fall into a sharp division between safety and ethics because I think the safety concerns are, of course, ethical concerns, but there are a lot of other ethical concerns as well.

DR. SHAPIRO: Thank you. Alta?

PROF. CHARO: Before I say anything, should I go on, let me just go on the record about the fact that back at Wisconsin I've had conversations with Jamie Thompson before he began his research about the separation of his research from Federal funding, and have been a member of a committee after his research was completed that was looking at it from the point of view of the university's interests. A question to Carol, and then a comment. Carol, you had asked Dr. Brinster when it is that the zygotic genome takes over, and I didn't understand what that meant or why that was significant.

DR. GREIDER: It was partly a lead-in to my second question, if we're getting to the, if people are going to be asking us is it possible for you to create a human with this bovine oocyte and a human nucleus, presumably you would have to implant that into some organism. And I was thinking that the antigens on the bovine cell would make it be rejected if you were to implant it into a human, and therefore it would not be possible to make it a human. That's what I was thinking.

PROF. CHARO: Thank you. The comment actually in some ways it's more of a question is probably directed mostly at David and Carol. I'm not sure. It seems to me that part of the analysis that one would want to develop for the President could focus on what this fused cell is most like that we already know. Is it most like two nongametic cells that are fused, or is it most like a regular human embryo, or is it most like something else? And as I listen to these things I'm particularly intrigued by your comments about uncertainties. I find myself thinking that the question is, would it be inappropriate to try to do that? Would it be most appropriate to say that this is something that is entirely new as a phenomenon and can't be analyzed by analogy to other entities and can't be conveniently slotted into existing schemes of either ethical discourse or regulatory treatment?

DR. COX: My view is, unfortunately, that's exactly the situation. I mean I think that this isn't simply another fusion of two somatic cells, nor is it an embryo

because we don't know that it even divides. Unfortunately, I believe it's closer to an embryo than it is two somatic cells, and I say that based on my view that the egg is a special type of cell.

PROF. CHARO: But its viability is severely in question, which is the key characteristic of embryos that drives all the debates about embryos.

DR. COX: So it's new, Alta, is what it is.

DR. BRITO: This question is for David and Carol to clarify something here that was reported in the *New York Times*, and I recognize this has not been necessarily scientifically proven. But what is the significance? They've discussed that at some, at one point the combination of bovine oocyte cytoplasm with the human nucleus becomes primordial and this is what is key in terms of it being able to form a stem cell that further divides. Is this something that's new in hybrid research, the fact that it can revert to a primordial state?

DR. GREIDER: I think that "pluripotent" is the word. Pluripotent, and that's what we were hearing from Dr. Brinster that you can get certain cell types, which is what the two papers that you were just given are about these pluripotent human embryonic stem cells that were reported, which will be our other issue. So the thought is that if you can take this bovine/human mixed cell type and differentiate it, you can get these pluripotent cells out, that would then go on to form something which would be mostly a human tissue type that could be used in medical research, muscle cells, neurons. And so the point is that you can make this pluripotent cell type from that initial fused oocyte.

DR. BRITO: Right. So the primordial reversion of this hybrid, is that something new?

DR. GREIDER: No.

DR. COX: No, that's been around.

DR. GREIDER: The thing that's new here is that it's two different species. The other thing that we're talking about is what we dealt with in cloning, which is taking a human nucleus and putting it into a human cell, and you can get those same cell types out there. The difference here is the convenience. It's easier to get these

oocytes from cows than it is from humans.

DR. BRITO: No, I understand that. But David was discussing earlier the fact that cells from different species have been -- this has been done for a long time, but I had never heard of different species being able to combine with the nucleus into an oocyte of different species within the cytoplasm.

DR. GREIDER: He's talking about cells from different species.

DR. BRITO: Yes.

DR. GREIDER: Somatic cell types -- you take two different somatic cells that are growing in culture and fuse those and study their properties. And that's David's area.

DR. COX: That's what cloning is, so that's what we talked about-- transfer cloning. I'd like to make it clear that it is unclear that this has happened between the cow -- the bovine oocytes and the humans. There is to me no evidence one way or another, because I don't get my science from the *New York Times*.

DR. BRITO: Right, but that's...

DR. COX: I will say, though, that it's not new, the idea of being able to take cells from different species, one of which is differentiated and one that isn't. So, for instance, a muscle cell of one species can take a lipocyte from another species and you can basically turn on muscle genes. So this idea of reprogramming by taking different types of cells at different levels of differentiation isn't a new one.

DR. BRITO: No, I understand. Thank you.

DR. SHAPIRO: I do want to tell the commissioners that Michael West is here. He performed this experiment we're all talking about, or referring to, and thinking about -- and have limited knowledge about. I think he was here. Is he still sitting in the back there? All right. And I only mention that to see if anyone has a question they would like to ask Dr. West, I'm sure he would be -- I'm not sure he may wish to answer.

DR. COX: Well, I would very much like to know what was done.

DR. SHAPIRO: Dr. West, would you want to just come and sit over here

until there is a microphone available, so you won't have to stand?

DR. COX: And I don't think that publication is the way one gets one's science.

DR. MICHAEL WEST: Right.

DR. COX: But oftentimes people describe to one another what the experiments were before they're published.

DR. WEST: Right.

DR. COX: And that hasn't happened here. So if you're willing to do that it would be extremely informative.

DR. WEST: Let me just say parenthetically here that we at Advanced Cell Technology had this debate internally as to whether we should proceed with this research as you know, this was done back in >95/'96, before Dolly or not do anything, or whether we should proceed with the work and do more work and then publish the data; or -- and, actually, I proposed it would be best for us to disclose publicly what had been done, even though it's preliminary, and even though obviously we'd get the criticism that this is not available for public review. But the data actually is published. It's in the European patent filing, and it is preliminary data. But we felt that -- at least I felt that it would be best for us to set a precedent here. This is a very controversial area, obviously, involving nuclear transfer, cultured embryonic cells, and so on. And right or wrong -- and we certainly will bear the criticism but we felt -- I felt that it would be better for us to disclose this data and talk about it openly rather than setting a precedent of saying, "Look, let's have science go on behind locked doors, and then do experiments out of the public view." And that is why we chose to release this information publicly in a premature state.

DR. COX: Dr. West, excuse me. Can I ask one question?

DR. WEST: Yes.

DR. COX: When you take human cells and you put them into nucleated bovine oocytes, how many times do the cells divide?

DR. WEST: Well, the research that was published in the European patent

filing was some 50 nuclear transfers, largely oral mucosal epithelial cells, but also blood lipocytes and fibroblast inter-nucleated bovine oocytes, again because we are a bovine cloning company and have large access to bovine oocytes. And again, as was mentioned earlier, the long-term thought here would be to supply a surrogate oocyte that could be humanized, so as to have human mitochondria as an accessible, inexpensive, and we believe humane alternative to animal source oocytes for nuclear transfer. Some 50 nuclear transfers were performed. In the patent filing we gave an example of one blastocyst formation. Most -- as with all nuclear transfers, all but 1 or 2 percent go to full-term blastocysts. We had similar numbers with the human nuclear transfer leading to one blastocyst, which when put in culture led to cells that flourished for a short period of time, and that had an indistinguishable morphological criteria of embryonic stem cells. As you know, there are numerous morphological characteristics: small cytoplasmic-to-nuclear ratio, prominent nucleoli refractile boundary, and so on. And we filed, based on that -- we had subsequent data and did replicate those results.

DR. COX: But if I understand that by nucleating bovine oocytes, putting in a human somatic cell of different types, then it 's possible, and in fact you, on more than one occasion, had blastocyst development.

DR. WEST: Yes, that 's correct.

PROF. CHARO: May I follow up on that?

DR. SHAPIRO: Yes, Alta.

PROF. CHARO: And then what happened? Did you actually stop any further development past the blastocyst stage, or did development -- normal development stop on its own?

DR. WEST: Well, the goal of this technology was to find a surrogate source of oocytes to deprogram human somatic cells for human therapy. Therefore, when the blastocyst stage was reached, the blastocyst was put in a culture, as is typical, to derive embryonic stem cell cultures.

DR. SHAPIRO: Thank you. Diane?

DR. SCOTT-JONES: Would there be a way that you could make available to us a copy of your report that you said you filed?

DR. WEST: Yes: it is in the public domain, and I can easily make that available yet today if helpful.

DR. SHAPIRO: That would be fine. If you would just send one copy to our office in Washington, we can take care of distributing it. We would really very much appreciate that. I don't want to -- I don't know what Dr. West's schedule is like, but since he's here, if there are other questions now would be a good time to ask, if there are additional questions. Yes, Trish.

PROF. BACKLAR: You said that you did replicate this. Can you tell us how many times you replicated?

DR. WEST: I know that it was replicated once. I am a little fuzzy on another experiment. I believe at least a blastocyst was achieved. I'm not certain about the embryonic stem cells.

PROF. BACKLAR: Were the numbers equal in the second replication with the attempt at one blastocyst?

DR. WEST: I believe they were roughly equivalent. And again, I would emphasize, these are approximately the numbers we see. We perform roughly 1,000 nuclear transfers a week in the effort to make cloned cattle that have produced pharmaceuticals in their milk. And those are roughly the numbers we get with bovine cloning as well.

PROF. BACKLAR: Okay. May I ask you one more thing? And that is, how are you funded for this research?

DR. WEST: It's entirely a private biotechnology firm.

DR. SHAPIRO: David?

DR. COX: Yes: one more question, moving to the evidence for human embryonic cells.

DR. WEST: Uh-huh.

DR. COX: So for those -- and you mentioned the morphologic characteristic. How many times were they passaged -- actually, I have three parts to this. How many times they were passaged; if an analysis was done to see if their chromosome

content was a normal diploid human chromosome; and third, were they ever able to be cloned from an individual cell? That is, once you have the stem cells, could you create the clones from individual cells?

DR. WEST: At the time these experiments were performed, the cells were analyzed only for these morphological characteristics. There were no antibodies in the laboratory to do state-specific embryonic antigen markers and other markers that are characteristic of ES cells. I think if we had those regions available, I'd perform those experiments. I think we probably would have had a publishable amount of data. That data was not available. Chromosome analysis was not done. However, the removal of the genomic -- nuclear genomic material -- is confirmed by staining under ultraviolet light. So we actually observe the removal of the nucleus, and, of course, the implanting of the human cell. We think it's highly unlikely that this was anything other than human cells, based on that.

DR. SHAPIRO: Alta?

PROF. CHARO: Dr. West, you mentioned humanizing the bovine mitochondria, if I heard you correctly.

DR. WEST: Yes.

PROF. CHARO: I wonder if you could explain what that means and what its significance would be.

DR. WEST: Well, we haven't talked about this just until recently for our own intellectual property reasons, but the goal here was not to mix species. And I think the President has justifiable concerns about mixing the species, as has been I think debated in the last 25 years from recombinant DNA technology all the way to the present day. The goal was to make a new technology available, which is based on human embryonic stem cells on the one hand and nuclear transfer on the other, and actually marrying the two together. So the thought would be, if we have a patient afflicted with a disorder where we need transplantable cells, we could take a body cell, de-differentiate it, use it in therapy, and it would be histocompatible. The remaining problem, of course, would be the source of the oocytes. And, in addition to the problem of sourcing the oocytes, we have quality control issues. If indeed this technology moves forward, sourcing human oocytes in large quantities would be a nightmare for the Food and Drug

Administration and for biotechnology doing quality control on 1,000 or 100,000 different women would just be most impractical. And so the thought would be, if we could source oocytes from a cloned animal, all would have the same genetic background, all could be kept in confinement. They could be well characterized and potentially, as we said, engineered by reverse nuclear transfer, for instance, to have bovine oocytes with human mitochondria. We believe it's possible. I could actually lay out how that strategy would be performed. And then when nuclear transfer would be performed, we'd have a fully human embryonic stem cell. I think that's an important point, which was not brought forward in any of the previous discussions today.

PROF. CHARO: So you would then -- you would be taking the enucleated bovine oocyte and turning it into a culture medium and nothing more?

DR. WEST: That's essentially right. As you know, we culture therapeutic cells today in the presence of bovine serum, which contains cow proteins. This is essentially no different from that. We believe that we would be eliminating all bovine genetic material, and simply incubating the human somatic cell in these embryonic bovine proteins to de-differentiate the cell, unlocking this pattern of gene expression, which would allow the cells then to differentiate into pathways currently inaccessible in medicine.

PROF. CHARO: And do you have anything at all by way of what could become a handout that explains the reverse nuclear transfer process that would humanize the mitochondria?

DR. WEST: Actually, I have some diagrams I brought with me today, which I'd be glad to pass around, which diagrammatically lay out this procedure, and I think make it clear how it could be performed.

DR. SHAPIRO: Okay. Well, if you could pass that out, I'm sure that would be helpful and instructive. But I think there may be some more questions. Diane?

DR. SCOTT-JONES: I have a question about whether you have thought through any of the possible ethical issues that arise with the research that you're doing. You've already said that you are not engaged in any of the kinds of things that President Clinton mentioned in his letter that might be possibilities of the notion of mixing species. But what do you see as the ethical issues that you face in this research, and what are

your thoughts on how you 'll resolve them, or how you 'll create in the public the view that you are behaving ethically?

DR. WEST: I appreciate that question. That 's a very good question and a very challenging one. By way of background, I was the founder of Geron, the company that made the -- that sponsored the work on the embryonic stem cell work. And there I formed an Ethics Advisory Board with members of the biomedical ethics community, in part because I believe that it 's important for biotechnology to be self-circumspect in this area. I think as we inevitably in the coming years have more and more sophisticated technologies, which raise more and more red flags, I think it 's absolutely critical to keep public trust and to have open and honest discussions. Forgive me for telling a personal story, but I read a newspaper editorial by an individual who wrote that science should stop so that ethics can catch up. And my personal ambition in biomedical research is to communicate to people in public policy and in biomedical ethics, so that, simply, ethics can walk hand in hand with science and science does not have to stop, because there is so much to be done in so little time. I do think there are -- these are very complex issues, as I mentioned, combining nuclear transfer technologies with cells that for all practical purposes are totipotent, the human embryonic stem cell. The only truly totipotent embryonic stem cell is the mouse, that we know of, and, possibly chicken, in that these cells can become everything, including the germ line. Cultured bovine and porcine and rhesus monkey and human appear to be ES-like in that, as you 'll see in our patent, we describe ES-like cells as meaning cells that have -- they are potentially totipotent, but they -- not in the case of human, but in the case of bovine and porcine -- when attempts are made to make them go germ line they do not form germ line tissues but are shown to make every other somatic tissue. So for all practical purposes, we believe these human ES cells -- at least the ES-like -- are potentially totipotent, or at least so close the only cell would not be germ line. So the ethical issues involved in such an important cell and what it means in human medicine, and also in many other respects the nuclear transfer to make those cells, and then on top of that the genetic modification of these cells creating cells in human cells and tissues that are transgenic. Many of these technologies have not existed before, and our hope is that we can simply have very intensive dialogue in the years ahead. And frankly, our hope was by announcing this preliminary data we could stimulate such discussions. We are not currently working in this area of technology waiting for consensus, and we would love to be able to feel comfortable with knowing

the guidelines as to how we could proceed.

DR. SHAPIRO: Carol?

DR. GREIDER: I just have one question with regard to what you were just saying. The term "totipotent," as opposed to "pluripotent" you were referring to these cells as ES-cell-like, and yet you used the term "totipotent." And I thought that we just established from Dr. Brinster that cells which do not form germ line are considered pluripotent. Is there a discrepancy here?

DR. WEST: Well, there is a bit of a discrepancy. Pluripotent is often used for the bone marrow stem cell, which can become many cells, the lipocytes and the granulocytes and so on, but not a neuron, not a myocardial cell. It's true that we could call the cultured human ES cells pluripotent because of their ability to form every cell in the body. Presumably, the only cell in question being the germ line, I question whether pluripotent is a good enough designation that you're right to be absolutely accurate, have not demonstrated their totipotency. Pluripotency certainly has been demonstrated.

DR. GREIDER: So that the information that you're going to give us from the patent application describes them as totipotent?

DR. WEST: ES-like, or potentially totipotent, I think, would be ideal from my perspective.

DR. LO: I have a question, which is both a definitional question and a conceptual question. As I understand it from Dr. Brinster's comments, he defines a totipotent cell as one that is capable of being differentiated into all cell lines, including germ cells. I take it that's in vitro, in the laboratory. Do we know what happens if you were to try to plant a punitive totipotent cell into the uterus of the species from which the DNA was taken?

DR. WEST: Yes. Generally, those experiments are the chimera experiments where you take a blastocyst embryo and then inject into it cultured embryonic stem cells and it forms a hybrid chimeric animal, sort of like a zebra, or half -- made of some -- parts of the body are made of one type of cell, and the other part made of the other. And you usually then sort out animals where the cells have contributed to the germ line to get animals that have been entirely genetically engineered. But in terms

of your question, okay, are these cells totipotent? Does that mean that they are capable of forming a pregnancy if injected into the uterus? All of the evidence suggests that they are not. That's an important point. These cells form a part of an animal, or indeed an entire animal if injected into a blastocyst where there is a trophoblast, a sphere of cells that form the placenta. These cells, the embryonic stem cell for a mouse, which we say is totipotent, or presumably the ES-like cells from other species, will not form a pregnancy if injected into a uterus. They are not totipotent in that sense, that they can lead to a pregnancy. Totipotency only refers to their ability to form the many different cell types in proper conditions.

DR. SHAPIRO: Perhaps I could ask a question that may be going over ground you've already covered. If so, I apologize. The question I have in mind is, in order to develop these various techniques given the objectives here, is it -- do the next steps on the scientific agenda over the next year, or two years or whatever it would be, really need to deal with human material, or is there a series of animal studies that you would choose to do first? And you perhaps have answered this question. If so, I apologize, but that wasn't clear to me. I'm worried about the next steps in the scientific agenda to achieve the objectives you're interested in.

DR. WEST: It's certainly true that research can proceed with purely animal studies as opposed to human. However, I think that, as you know, in the United Kingdom a distinction has been made in nuclear transfer work between therapeutic cloning and reproductive cloning. And I think it may be the truest course in most of the human interest to allow human cell therapies to develop unencumbered at a maximum rate for lack of fear that our attempt here is to clone a human being. I think it's clear that there are straightforward research objectives here: to make important stem cells for human medicine that would not run the risk in any way of facilitating the cloning of a human being.

DR. SHAPIRO: Thank you. Any other questions? Yes?

PROF. CHARO: A quick clarification, Dr. West. We just all received a handout called "Comparison of Methods for Generation of Human ES Cells." This is not the diagram about reverse nuclear transfer.

DR. WEST: That's correct.

PROF. CHARO: Okay. That ' s a different one that will be coming around eventually?

DR. WEST: That diagram just compares the human ES cells as described by Dr. Thompson and Dr. Gerhardt....

PROF. CHARO: Right.

DR. WEST: ... versus an autologous ES cell made by nuclear transfer.

PROF. CHARO: Have you been working on the humanization of mitochondria for the past three years, or is that an extremely recent area of interest?

DR. WEST: Well, it ' s a long-term area of interest, and we have not begun any work really, but we would like to proceed in that area.

DR. SHAPIRO: Diane, Carol, and Tom.

DR. SCOTT-JONES: This is just a question to ask you what this is so we ' ll know how to identify it -- I mean the source of it should we reference you what the source of it is?

DR. WEST: That ' s from Advanced Cell Technology, correct.

DR. SCOTT-JONES: I ' m sorry?

DR. WEST: That ' s from Advanced Cell Technology, to clarify how the technology that we ' re describing compares with the science paper and the PNAS paper that just recently came out. The first diagram on the left describes the approach of making human embryonic cell therapies by nuclear transfer using a surrogate oocyte. For instance, a bovine oocyte that ' s been humanized to have human mitochondria. The second diagram describes the sourcing of embryonic stem cells that are not autologous. "Allogeneic" is the terminology meaning from another human being, essentially another embryo from in vitro fertilization. And therefore there are issues regarding histocompatibility. And the third describes cells sourced from the gonadal ridges of developing fetuses, the embryonic germ cell or embryonic stem cell as described by Johns Hopkins.

DR. SCOTT-JONES: I ' m sorry. I just missed the first part of what you

said. I just wanted to know how to reference this: is it from your company, this diagram?

DR. WEST: Yes. Advanced Cell Technology prepared that diagram.

DR. SCOTT-JONES: Okay.

DR. SHAPIRO: Okay. We're going to have to bring this part of our discussion to a close here with Carol.

DR. SCOTT-JONES: Actually, David is the one who wanted to ask a question.

DR. COX: Two very quick questions. The first deals with this diagram, too.

DR. WEST: Uh-huh.

DR. COX: Is it in fact the case that you demonstrated that, by the ACT technique, that stuff is a fully compatible transplant?

DR. WEST: No, that's purely based on biological theory. The concept is -- I'm sorry?

DR. COX: It's theoretical, as the question mark is there, and the other approaches are theoretical but they are incompatible transplants, right?

DR. WEST: Yes. It's based entirely on the belief that not only major histocompatibility antigens but many other minor histocompatibility antigens pose certain problems associated with allogeneic grafts.

DR. COX: My second question is a more complicated one and in some ways unfair, so I don't mean it to be sort of an "in your face" question. But there are a lot of people who feel very strongly about embryo research in this country, and it provides them zero solace that you're not going to take these blastocysts and use them to try to create an organism. And so what would you say to those people?

DR. WEST: Well, what I would refer to is to the mention of fire. Fire, as you know, is a powerful source for good or bad. And I'm sure in the early days those who invented fire noted that it could be used to cook food and prevent food poisoning, and to heat their homes, and save lives. On the other hand, it can burn your house down.

Our intent here is to find all of the good applications of these technologies, accelerate them as much as we can for the treatment of human disease and to alleviate human suffering, and at the same time make the world the type of place that we want to live in.

DR. COX: Do you have any recommendations about how we might prevent the bad from happening while allowing the good to go forward?

DR. WEST: Well, I think, as in the United Kingdom, a decision to potentially criminalize or make other prohibitions against the cloning of a human being may be a good first step.

DR. COX: Thank you.

DR. SHAPIRO: Thank you very much. Tom, you had a question?

DR. MURRAY: Well, actually, David asked pretty much the question I wanted to ask him. I thought your answer was not -- I'm sorry -- was not very good at all. I listened carefully to the answer, and I just thought it was a terrible analogy.

DR. WEST: Remind me of the question then.

DR. MURRAY: Well, the question. There are people out there in the United States who are morally offended at the thought of any research on an embryo, and probably even moreso -- well, certainly even moreso -- at the notion that one would create a human embryo for the purpose of doing research on it. We just have to acknowledge that that's a fact about the United States. That is why Congress told NIH it may not fund any research on human embryos, and that has had some -- that prohibition on funding has had, in the opinion of some of us, some fairly deleterious impacts on the quality and the ethical review of some research. I have to be honest about that. You responded with the analogy of fire. That's just not going to comfort any of those folks. It's not even really going to respond to their concerns. Their concerns are that embryos are, to them, the same as a person. And is there any answer we could give? I take it what I'm hearing is that the constructs that you're creating by using the bovine oocyte in the human nucleus might in fact be meant to avoid this problem.

DR. WEST: Well, I think the nuclear transfer technologies have demonstrated that potentially every cell in the human body has the genetic potential of becoming a human being. And so....

DR. MURRAY: They're not all sitting inside oocytes.

DR. WEST: Yes, that's correct.

DR. MURRAY: It's a big difference.

DR. WEST: That's correct. And I think that the -- that all of these technologies together, I think, have brought us to the point where we as a nation need to think long and hard about what is our stance toward the fertilized human zygote, the morula and the blastocyst. And I think there are many points of reference here. And I think all of them need to be carefully considered hand in hand with the medical benefits gained from using these technologies. I don't mean to be evasive. I'm thinking I'm probably telling the Commission things that the Commission already knows. I think the word "embryo" carries with it a lot of connotation, a lot of emotion. I think much of that emotion is well-placed. I think human life is a sacred thing. I think a developing embryo and fetus should have a status more than just a conglomeration of cells. But when we get back to the point of a somatic cell, if we took this to the point where we believed that every human somatic cell was a human being, had the potential to be a human being....

DR. MURRAY: That's an argument.

DR. WEST: But that's a....

DR. MURRAY: I agree. I appreciate it. I think most of your answer has been responsive, but I really would like to know, in your opinion, whether the constructed, created bovine, the nuclear oocyte in the nucleus, is potentially a viable human embryo.

DR. WEST: I would be glad to give you my personal opinion. It's just that, but my personal opinion is that up to the stage of gastrulation, the embryo, if cleaved in two, leads to identical twins and therefore at that stage of development there is no individualization. Otherwise, you would have somehow cleaved the being into two people. And after gastrulation there is sort of a line drawn in the embryo. There is a point at which differentiation is begun. At that point, if you divided the embryo you would get a phenomenon like Siamese twins, or other developmental abnormalities. And there was a sort of general rule in in vitro fertilization that embryos up to gastrulation have a

distinct status from embryos after gastrulation. All of these technologies would involve the development of small aggregations of cells, the blastocysts prior to gastrulation. And if you ask my personal opinion, I would suggest that we should draw a line in the sand where the embryo draws a line at the primitive streak stage, and suggest that nuclear transfer to make primitive cells up to -- or embryos up to the point of gastrulation should be considered under certain carefully circumscribed uses for medical benefit.

DR. MURRAY: You've actually conflated two things, identity and viability, and I understand the argument. I'm familiar with those arguments, but I take it, at least by inference, that you think such constructs that you created might in fact be viable whether or not they split. If they split they might be two viable embryos, but it might be viable. Am I advising correctly?

DR. WEST: I'm sorry. Could you clarify that question?

DR. MURRAY: I think that's -- I think we're -- that's all right.

DR. WEST: Okay.

DR. SHAPIRO: Okay. I want to thank you very much for being here and for being so candid and responsive to us, to the questions of the Commission. I very much appreciate it. We're going to take approximately a 20-minute break now, and then we will do public comments after the break. So please, at 3:30 I'd like all commissioners back, since I do want you to be here for the public comments.

## **PUBLIC TESTIMONY**

DR. SHAPIRO: There's been some flexibility in our agenda, and what I propose to do now is go directly to public comments. We have two or three people who want to speak to us in public comments, then we're going to adjourn the meeting until tomorrow to allow the people who are going to do some writing for us to get down to their work so they won't have to be writing until 2 or 3 o'clock in the morning. So if you don't mind, we'll get to the Biological Materials Report in the morning.

I'd like now to begin our public comments. I'm not sure if Dr. Shellow

is still here; is Dr. Shellow here?

DR. MESLIN: I believe he had to leave.

PROF. BACKLAR: I don't see him, no.

DR. SHAPIRO: Okay, Dr. Michael Guarino? Welcome. Walk right up. It's very nice to have you here. Thank you for coming.

MR. MICHAEL GUARINO: Thank you, but I'm definitely not a doctor. I'm here today to represent the Autism Society of America and also as a board member of the Autism Society of America Foundation. I'm here to talk about what you finalized here today, your research findings on persons with mental disorders. But most important, perhaps, I'm a father, the dad of an eight-year-old child who's non-verbal because of autism, and every day I do research on my little girl: from AIT, Auditory Integration Therapy, to behavior modification, occupational therapy, physical therapy, speech therapy, swimming with dolphins, [UNINTELLIGIBLE], music therapy, and the latest, quote unquote, "cure" for autism, secretism. I come in front of you because autism is one of the most complex and elusive neurological disorders facing the biomedical research community. While the Autism Society welcomes the Commission's work on behalf of people with impaired mental capacity, if it's implemented in its current form there will be a dramatic reduction in ongoing neurological research. My two major points have to do with two of the recommendations you adopted today was Recommendation 12 in the report, which talks about [UNINTELLIGIBLE], and that pediatric research was excluded in Recommendation 12. I would just like to see somewhere in the language, if not in the recommendation itself, but it in the language underneath it, so you'd be able to explain that the researchers in autism haven't found what they seek yet, that it's been an issue.

DR. MESLIN: I'm sorry to interrupt. Could you say that last bit just one more time, a little more slowly?

MR. GUARINO: In Recommendation 12?

DR. MESLIN: Yeah.

MR. GUARINO: For pediatric research being done with children with children with autism that is excluded from these criteria.

DR. MESLIN: I understand the point.

MR. GUARINO: Yeah, that's what we were talking about. And the other one was on Recommendation 15. I know that you've worked hard on this and you're talking about possibly not making that recommendation. I think it's real important that families do have that option just still to be at the table with the people. I think that just not to be excluded from them, that's very important. And that's why I came down today. And just don't take the steps just to cut us out. We want to be involved. We're looking for the researchers to help us along the way. We're going to help partner with them. Thank you for your hard work.

DR. SHAPIRO: Well, thank you very much, and thank you for coming today and speaking to us. Thank you also for being so terse and to the point on a long day. That's very helpful. I appreciate -- I very much appreciate that you remained. Thank you very, very much. The next person I have is Dr. David Shore.

DR. DAVID SHORE: At this point, I feel like I'm asking a question from English class during the middle of a math class, but I'll try and get back to what was being discussed this morning. I think probably the best use of my five minutes would be to just try and get on the record and the transcript some brief reactions and a few questions, and some concerns that people I've discussed the most recent draft with at NIH have expressed. First of all, let me say that the people with whom I spoke were very impressed that this most recent version has made the most positive steps of any change during the previous meeting. And for that reason, many people are sad that you are finalizing it at this point, because there was the hope that perhaps NBAC could reach some conclusions that would not be argued with by the scientific community, but we'll have to see what happens in that regard. Certainly, I think you're at the point now where most at NIH would agree with the majority of the recommendations that you have. The major concern that I think people will have is Recommendation 2, the RAPID. If this were to be a board that were to discuss policy issues, rather than protocol-by-protocol or case-by-case reviews, I think we might not have as many concerns. But if it looks like what you're doing is creating a national IRB to take away from the local IRBs their authority to make certain decisions that they now have, I think there is considerable concern that it will take time to charter that group, to staff it, and that the term "RAPID" may not actually apply to the process by which protocols are considered.

If the board is to do research, certainly there are groups like IOM that can gather data that can answer some of the scientific questions that have been raised. But I think there is concern about creating another level of bureaucracy that will look over the shoulders of local IRBs.

The third and final major concern that we have is that both the title and the text still focus on mental disorders. And as we have expressed repeatedly, and I know Dr. Shellow was going to comment on, and I believe he's given you some written remarks, of course, most people with mental disorders do not have questionable or impaired capacity, and most people with impaired or questionable capacity do not have primary mental disorders. And therefore we have been arguing over time that to call this a report on mental disorders that may impair capacity is really quite misleading, that you're really talking about people with autism, people with mental retardation, people with Alzheimer's disease, people with brain tumors, and that the conflation -- that's a popular word today -- the conflation between mental disorders and impaired capacity is, I think, inappropriate and unfair. And I would hope that it's not too late to undo that.

Just a couple of little minor points about the text in Chapter 5. I am still looking for the language about consent waivers and the circumstances under which they would be granted, notwithstanding discussions at the previous meeting. I still can't find them. And some of the recommendations that were voted upon today are directly inconsistent with the possibility of allowing consent waivers under the conditions in which they're currently allowed. It's unclear what happens until this RAPID board is created. Do we stop all such research for two or five years, or do we allow it to continue until the board is able to review, protocol by protocol, what will be allowed and what will be prohibited? As was already pointed out, we really don't have adequate competency assessments yet. And, clearly, we need research and time to develop them, and that's happening already. It's not so clear to me what's going to happen in the time that it takes to develop this board, conduct this national IRB function, and do the scientific studies to inform its reports. So, again, I think that this version is clearly getting closer to the versions that the scientific community would be able to support. But I think it helps a lot more for me to focus on the areas of disagreement in this context, than on the areas on which we agree.

DR. SHAPIRO: Thank you very much. Any questions? Yes, Alta?

PROF. CHARO: Dr. Shore, the recommendation -- I think it was 7 -- I no longer have my text in front of me, because I handed in my edited version -- was the one that said that no person with the capacity to consent can be enrolled without having exercised informed consent. The very first sentence of the text that annotates that recommendation repeats that, and then puts in the clause, "except where consent is waived. "Thank you. Now, do I understand correctly that what you would like is to have that sentence expanded to say, "except where consent is waived as per regulatory requirements for consent waivers in general" ?

SHORE: I guess it would help if it were up front and a little clearer earlier on that you 're not saying everybody with impaired capacity must give informed consent, or their legally authorized representative must. It is clear that the current regs allow for consent waivers under the three or four conditions that you 're well aware of. I would hope that that would be made clear, so that local IRBs, which may be concerned about greater than minimal risk, nontherapeutic research did not also get the message that they 're not allowed to provide consent waivers in the future.

PROF. CHARO: Okay.

DR. SHORE: That would help.

DR. SHAPIRO: Thank you. Thank you very much. Excuse me. Bernie?

DR. LO: If I asked you a question about RAPID -- you spoke about your concerns about a transitional period, and sort of a startup period. Assuming that it gets off the ground and is chartered and funded, do you also have concerns about its ability to function as sort of a national IRB clearinghouse? Did I hear you to suggest that you thought that was a less desirable function than the sort of setting of categories that the local IRBs could then use to apply to their deliberations?

DR. SHORE: Well, I have several concerns. For one thing, it kind of turns on its head the whole concept of local IRBs making decisions based upon local standards. And it creates a new centralized bureaucracy to decide what will or would not be approvable. And I think that that 's a dramatic difference from what we have now. I think that the potential delays were discussed at a meeting a couple of weeks ago on central review of multisite trials, in which they talked about a situation in Great Britain in which they have tried some of these regional or national IRBs and the response, the

back-and-forth between local and national IRBs was described as "chaos." So I would urge you to learn from some experiences in other countries that may have tried something similar and perhaps discovered that this may not be as easy as it sounds.

DR. SHAPIRO: Larry?

DR. MIIKE: Just thought I'd point -- the intent was that the -- at least my understanding of what I would like to see is that the national review protocol-by-protocol was an interim measure until more general guidelines could be developed. And so the responsibility primarily rests again with the local IRB. So I don't see it as a permanent situation. It's just that I think some of us were uncomfortable about moving toward that second phase immediately, just to build up the experience, or as Dr. Cassell was talking about, some registry of local board kinds of decisions. So there may be a transition factor. The other side -- another issue is, what's going to happen in the meantime? As I understand it, ours are recommendations. So it's not like we prohibit everything from happening until certain things are put in place. Ours is a recommendation, and we expect a reasonable transition to the kinds of things that we suggest.

DR. SHORE: All right. I think you're certainly right that there are discussions of classes of research, I think under (b), whereas under (a) it clearly starts out protocol-by-protocol. And given our concern about how long it takes to charter a committee, how long it takes to staff a committee, how long it takes to do the research needed, that we're realistically talking about upwards of five years before you can consider enough protocols to perhaps come up with a policy for even one technology. And it's unclear what happens during those five years. Certainly, if you were to make clear in your report that until this newly created board, or national IRB or whatever you choose to label it, that until such a Board has made decisions as to what decisions should be permitted locally and which should not be permitted locally, that the local IRBs can retain their autonomy, that would certainly go a long way towards allaying the concerns. But at present I'm unable to find any language that indicates what will happen during that potentially very lengthy interim.

DR. SHAPIRO: Alta?

PROF. CHARO: First, I just want to let you know that some quick

redrafting has gotten your concerns about the consent waivers in both the recommendation...

DR. SHORE: Great.

PROF. CHARO: ...on minimal risk research and the text following recommendation 6.

DR. SHORE: Thank you.

PROF. CHARO: On the latter point, though, I've got to say that you're touching on something that's more than just an operational issue, because for those of us that find the current local IRB exercise of authority to allow surrogate decisionmaking under these circumstances to be something that is inappropriate, to have it continue while people work on a board just continues a behavior that some of us feel is inappropriate. And in fact the board is something we see as an avenue to allowing IRBs to do something that otherwise would be inappropriate for them to do. So I think you've touched on something that's more than just a logistical question. I think it goes right to the heart of the debate about the rightness and wrongness of this research.

DR. SHORE: Well, I think that that's why we presented, at the last board meeting, the several pages of examples of what we consider to be important types of research on disorders, again, ranging from autism to Alzheimer's disease and certainly schizophrenia, bipolar disorder, that could not have been done had you in effect ruled out greater than minimal risk non-therapeutic research. And if you want to stop that for five years, I think that you should be aware that the kinds of research that we reported previously is going to be in jeopardy. If that's what you want to do, you can do that.

DR. SHAPIRO: Well, thank you, although I reserve the right to characterize what we want to do myself. Any there is no one else for public comment? What I'm going to do is adjourn the meeting. There's a small group that's going to be doing some writing on the issues. That's what we'll deal with again tomorrow: a response to the President's letter. So I think we'll adjourn for this afternoon and reassemble tomorrow morning at 8 o'clock.