

1  
2  
3  
4  
5  
6  
7  
  
8  
9  
10  
  
11  
12  
13  
  
14

24TH MEETING  
NATIONAL BIOETHICS ADVISORY COMMISSION  
October 20, 1998  
Holiday Inn-National Airport  
The Grand Ballroom  
1489 Jefferson Davis Highway  
Arlington, Virginia 22202

Tuesday, October 20, 1998  
**Welcome and Overview of Agenda** . . . . . **2**  
Harold T. Shapiro, Ph.D.  
  
**Discussion of Commission Draft, Research Involving Persons with Mental  
Disorders That May Affect Decisionmaking Capacity** . . . . . **5**  
James F. Childress, Ph.D. and Commissioners  
  
**Public Testimony** . . . . . **47**

1 **Welcome and Overview of Agenda**

2 DR. SHAPIRO: We'll get the meeting started. I'd like to call our  
3 meeting to order.

4 Quite aside from the public comment section, which will come later on  
5 this morning, the sole item on our agenda today is further consideration of our report on  
6 research involving persons with mental disorders. We often call it the Capacity Report  
7 just as a shorthand. Let me say a few things by way of introduction and then indicate  
8 how I'd like to proceed through the day, what I hope for from today and what that  
9 means regarding our schedule with respect to the final approval of this report.

10 First of all, I would like to say that in many ways the public comment  
11 period has been extremely helpful. I want to go on the record to express my  
12 appreciation for the many thoughtful comments we received from a large variety of  
13 sources—interested parties who care about what it is that we will be recommending and  
14 are saying about this subject. So I am really grateful to all of those who took the time  
15 and effort to read what we had to say and respond to it in ways that seemed appropriate  
16 to them.

17 I also want to indicate for the record, however, that there are interests out  
18 there which are not beyond intimidation to try to make us adopt views which they  
19 espouse. And while people are welcome to say whatever they like to us, I am not  
20 especially moved. Indeed, my resolve is further increased by the kinds of intimidating  
21 vocabulary and conversations that some people have engaged in.

22 So that's a small thing. I mention it only to inform the Commissioners.  
23 It's not really critical. Much more important is the thoughtful public comment we have  
24 received, which I think is not only important but will certainly improve our final report.

25 Now let's go directly to the schedule. As you know from the e-mail that I  
26 sent you, I can't remember if I e-mailed or faxed you or did both, but I had hoped that  
27 we would go through all of our recommendations today and come to consensus on them  
28 if consensus was available; or if not, to just decide where the majority of the Commission  
29 stood on the issues, inviting minority opinions if any, and to add dissenting comments or  
30 personal statements of one kind or another to our report. I think we still will do that in  
31 part; however, as I've read the report carefully and considered carefully all the written  
32 comments that we got, it seems to me there are some outstanding issues which we may  
33 not be able to fully resolve today. And so while I'd like to go as far toward resolution as  
34 possible, I think we're going to have to do some redrafting and pass that back before the  
35 Commission before I would feel comfortable asking you to sign off on it. I very much  
36 regret that because I think it is time to have our say and see what impact it has and not  
37 wait indefinitely. There are lots of people out there who want us to hurry; there are

1 other people who want us to wait. We have to have our own agenda here.

2 And so, my own thinking right now is, given the realities that we face and  
3 the necessity to give some thoughtful consideration to some issues, is that our final sign-  
4 off on this report probably will not come until our next meeting, which is scheduled in  
5 Miami for the 17th, I think. Arturo, is it the 17th?

6 DR. BRITO: The 18th, the 17th and 18th.

7 DR. SHAPIRO: The 17th and 18th. We have other items scheduled for  
8 that meeting, but I'm hoping really by that time, that meeting, that we'll have very short  
9 discussions of this report because the material which will be distributed in advance will  
10 have taken advantage of today's meeting. So I think while I'm disappointed in some  
11 sense that we can't reach decisions on everything today, I hope we'll reach decisions on a  
12 lot of issues today and then go from there and have a final sign-off probably at our next  
13 meeting in Miami.

14 I propose that we proceed in certain ways today. I don't want to begin by  
15 just going through the report chapter 1, chapter 2, and so on. I don't think that would be  
16 effective. What I want to do is I know many of you, as I, may have a large number of  
17 editorial suggestions, and there is some evidence in the current draft of word processor  
18 space where phrases and paragraphs sometimes find themselves in unusual places, and  
19 there are still a few like that here. But I really would ask us not to concern ourselves  
20 with that issue today; that is, we would be happy to incorporate or receive from you  
21 marked-up copies that are legible, or memos if that's a better way for you to  
22 communicate, which deal with all the editorial suggestions and we will go through them  
23 all and try to produce as good a document as we can. So I don't really want to consider  
24 those types of things unless they have some substantive implications for the issues that  
25 we're talking about.

26 I have gone through this page by page with Eric earlier this week and I  
27 have many such recommendations myself, and I'm sure many of you will have others.  
28 I'm very anxious that you give them to the staff so that we can incorporate them as fully  
29 and as clearly as possible.

30 Now as to today's meeting, there will be, as you'll see, a series of issues  
31 which we have to confront. But what I would propose we do is as follows. I want to go  
32 directly to the recommendations and that will generate other discussion. But I want to  
33 go directly to the recommendations and I really want to take the first seven or eight  
34 recommendations as the first items of our business. I want to see what, if any, concerns  
35 remain regarding those particular recommendations. We could take probably as a group  
36 recommendations 1 to 7 because it's only with recommendation 8 that we get into  
37 protocols with greater than minimal risk.

1                   Once we do that, we'll go through that, that will be our first item of  
2 business. Then I want to move on to an issue which is not a recommendation but I think  
3 needs to be a recommendation, and that is we don't say anything directly in the  
4 recommendations themselves about minimal risk research. We have a lot to say about  
5 the text. But I was kind of surprised when I read it over myself that this was, in fact, the  
6 case. I think it's pretty clear what we want to say and I think we'll try to draft something  
7 during the day while we're here today about that. But I think the report lacks a  
8 recommendation regarding our saying directly what we think is appropriate minimal risk  
9 research. We'll try to draft that sometime during this morning but we might have some  
10 initial discussion of it early on this morning.

11                   Then I want to go to the issue of the health care professional, which  
12 deals with when we think that is required and when we think that's simply something that  
13 IRBs might want to consider. That's unclear in my mind; I think it's unclear in the text,  
14 actually, because when we talk about it early on around page 86 or so we have a rather  
15 different characterization of it than we do on page 151 where we're dealing with  
16 guidance to IRBs. Don't take those pages seriously, those are all approximate. I don't  
17 have this locked in my memory in some photographic way. And so we'll deal with that  
18 and then we'll proceed on to other issues.

19                   But that should give us a start. Let's try to be conscious today of the fact  
20 that we do want to make progress, we must make progress toward completing this. We  
21 must reach agreement on the great bulk of this before we leave today. If we come down  
22 to an issue where we think something needs to be redrafted or drafted, we'll take a recess  
23 and draft as opposed to just sitting around and discussing it further. We'll form one of  
24 our famous little buckets and we'll draft language and then come back and look at it.  
25 Because I just think we have to force ourselves into a discipline like that today in order  
26 to keep control on our path of march.

27                   So with that, unless there are any questions, we'll just go directly to the  
28 recommendations and begin dealing with them. We're going to see what further  
29 comments and questions there are. As soon as we get a recommendation that seems to  
30 be coherent before us, we will just see what the sense of the Commission is on those  
31 recommendations. And, again, I'm not going to worry right now about the text that  
32 surrounds some of these recommendations.

1 **Research Involving Persons with Mental Disorders That May Affect**  
2 **Decisionmaking Capacity**

3 DR. SHAPIRO: But let's go to the recommendations themselves. Jim, if  
4 it's all right with you, we'll just begin by going to Recommendation 1. Is that all right?  
5 This has to do with the IRB membership issue, if anybody wants to recall what that's  
6 about. It is on page 121 in chapter 5. And for each one of these, I think, I will ask Eric  
7 to just remind the Commission what we have heard or what issues have come up during  
8 the public comments just in case you want to know about them. We haven't gone back  
9 to Recommendation 1 in quite a while. Do any of the Commissioners have any concerns  
10 or comments they want to make regarding Recommendation 1? This is what I call the  
11 IRB membership issue, but however you want to describe it.

12 DR. CHILDRESS: I might just add this is one we, by and large, received  
13 positive response to, though I think many of those who favor the recommendation would  
14 be happier if it were a matter of guidance rather than a regulatory requirement. But I  
15 think the substance of this particular one seems to generate a positive response.

16 DR. SHAPIRO: All right. Then I'll assume that Recommendation 1 is  
17 something we'll just go ahead with. Again, any editorial or other comments regarding  
18 just how this is described in the text and so on, please pass on to the staff.

19 PROF. CAPRON: Could I, Mr. Chair?

20 DR. SHAPIRO: Yes, certainly.

21 PROF. CAPRON: Steve turned to me as you were making your opening  
22 remarks and asked vis-a-vis the one remark that was the most delphic what was going  
23 on. So let me put my own question before you. Whether the question is principally that  
24 the psychiatric community is unhappy with the report. And the reason it comes up with  
25 Recommendation 1 is that I believe that some of the objection that we heard early on  
26 was that any singling out of people with any particular disease category and saying that  
27 they are in need of extra protection here by being made members of the IRB is a form of  
28 stigmatization of that group. So it's a compound question, Mr. Chair.

29 DR. SHAPIRO: Delphic is my own remark.

30 PROF. CAPRON: Is the objection that keeps us from being able to  
31 progress to conclusion on this, other than the absence of the one recommendation that  
32 you mentioned that we need to address about minimal risk research, is it that we have  
33 got to refine or revise in light of objections from the research community? And if so,

1 what about this first recommendation, is it not subject to the same objection? Or did I  
2 entirely misread your delphic—

3 DR. SHAPIRO: My delphic remarks come from all sides of the issue;  
4 that is, it is not confined to any one community. I wouldn't want to characterize any  
5 community as having any uniform views on these matters. But it came from all sides;  
6 that is, some people thought we were being nowhere near demanding enough, and others  
7 who thought—and it didn't relate to this recommendation. I will highlight any  
8 recommendation it relates to. It did not relate to this one as far as I'm aware.

9 PROF. CAPRON: I understand it did not. But I should say, because I  
10 believe we have to be open about these matters, that I was approached by several  
11 members of the psychiatric research community at a meeting I was at last week who  
12 described to me a process of addressing with the Commission, both out of the National  
13 Institute of Mental Health and out of leaders from the psychiatric research community,  
14 their unhappiness with this and, in particular, some views attributed to me which they  
15 thought made me a good candidate for their services. And since we hadn't had those  
16 views from those people ever in writing or in public comment before, I was not surprised  
17 to know that they were being voiced to us rather strongly.

18 But it seemed to me that the logic that I was hearing from them was that  
19 any attempt to single out a group of subjects and treat them differently bordered on  
20 stigmatization because it took at view that this was a vulnerable group needing  
21 protection of some sort and that that's an old-fashioned view that buys into all the  
22 prejudices about mental illness.

23 DR. SHAPIRO: That view has certainly been expressed. We discussed it  
24 last time we were together when we discussed the scope of this report. That wasn't the  
25 one that was especially on my mind.

26 PROF. CAPRON: And their further statement is that there is no objection  
27 that we know of to the insistence that IRBs that regularly review would always have and  
28 have present at their meetings where they deliberate on such protocols this sort of  
29 representation.

30 DR. SHAPIRO: That's correct.

31 Jim?

32 DR. CHILDRESS: Well, on your distinction between guidance and  
33 regulation, I think there's very little objection to this being offered as guidance. There is  
34 objection to it being offered as a regulatory requirement.

1                   PROF. CAPRON: But I said the substance doesn't seem to be as  
2 problematic as what kind of form is this recommendation going to take.

3                   DR. CHILDRESS: That's just one person's impression having looked at  
4 the comments and talked to a lot of people. Maybe Eric has a response as well.

5                   MS. FLYNN: Could I offer a comment here because this  
6 recommendation, which I'm very, very pleased with, is very similar to a recommendation  
7 that my organization adopted as policy in 1995 and forwarded to all academic  
8 institutions' departments of psychiatry that were actively engaged in research. At least  
9 while there are many other parts of this report that some members of the research  
10 community may have concerns about, Alex, I think I'm fairly confident in saying that I  
11 don't think this is one of them.

12                   The feedback I've received as recently at a meeting of biological  
13 psychiatry a couple of weeks ago is that this is really in fact a linchpin of ongoing  
14 support and protection for vulnerable human subjects. Putting representatives in the  
15 room on the IRBs when such protocols are developed and discussed I think is accepted  
16 very broadly in the research community. I've had literally no one in that community  
17 come up to me and complain about this one.

18                   I have had, interestingly, a colleague who is active in breast cancer  
19 research, and you do hear from folks who move to the issue of will we have the  
20 balkanization of IRBs, we will have a drive to include subject representatives in a variety  
21 of areas. And I suspect we will and I don't necessarily think it's a bad thing to consider  
22 those issues for other potentially vulnerable or high-risk populations.

23                   DR. SHAPIRO: Thank you.

24                   PROF. CAPRON: What I wonder then is if the recommendation has  
25 generally in your experience met with such a good reception in the community, and given  
26 the fact that for all the reasons that we talk about in the report the subject population has  
27 vulnerabilities which may not characterize all other balkanized different disease  
28 populations, as it were, why is it that we do stop short of saying that this is a change that  
29 the OPRR should insist upon as it has insisted in cases in which it has found problems to  
30 exist? In other words, why not regard this as something that is prophylactic in its effect  
31 and not wait for another institution to have the sorts of problems that arose, for example,  
32 at UCLA?

33                   Would you like me to move that we make this a stronger  
34 recommendation? I'm not sure what—

35                   DR. SHAPIRO: That's right. If you think—

1 MS. FLYNN: I would support it.

2 PROF. CAPRON: Then I would so move that our understanding of  
3 "should" here or whatever changes in language are necessary to make that the case, that  
4 this become a recommendation for action rather than for advice.

5 DR. CHILDRESS: It is a recommendation for regulation.

6 MS. FLYNN: Yes, I do not read it as offering a choice.

7 PROF. CAPRON: I had, too, but then I thought I was being corrected by  
8 you earlier.

9 DR. CHILDRESS: No, no. I've said the agreement has to do largely  
10 with substance. But there's a lot of disagreement about whether this should be offered as  
11 a recommendation for regulation versus guidance.

12 PROF. CAPRON: But the shoulds and the shalls mean that if—

13 DR. CHILDRESS: We're offering this for regulation. It's clearly in the  
14 regulation section.

15 MS. FLYNN: We've already taken the stronger stand on that.

16 PROF. CAPRON: Well, that was my understanding and I thought from  
17 your comment, Jim, that I had simply misread it. We didn't say "OPRR shall require  
18 that..." but that we were somehow saying this is the ideal world. Then I have no  
19 problem with it.

20 DR. SHAPIRO: Any other comments on this?

21 Let's go on then to our second recommendation which I call, perhaps  
22 unkindly, the targeting regulation. This is so short I can read it to everyone. "An IRB  
23 should not approve research targeting persons with mental disorders as subjects when  
24 such research can be done with other subjects."

25 Any concerns regarding that recommendation?

26 MS. FLYNN: I believe I read in this one some clarity that I think we had  
27 wanted, that this does not preclude individuals with mental disorders from participating  
28 in such research on other health conditions that they may be afflicted with by virtue of  
29 their having a mental disorder. I felt good about the way this came through clearly.



1 DR. SHAPIRO: That's exactly right. Thank you for mentioning that  
2 again. I think it was the reason why the word "targeting" got into this phrase as opposed  
3 to its original draft.

4 Okay. Let's move on to Recommendation 3, subjects' refusal to  
5 participate, et cetera. This is too long for me to read, besides which all of you have read  
6 it. I think in the last times we've discussed this there seemed amongst the  
7 Commissioners to be little concern about this, nor did I pick up any serious concern  
8 about this reading the public comments.

9 DR. DUMAS: My only concern is that it's rather long and there's a vague  
10 statement at the bottom having to do with reapproaching previously dissenting persons.  
11 There's some concern about how many times people should be approached and when it  
12 borders on coercion.

13 DR. SHAPIRO: Eric?

14 DR. MESLIN: Just to remind the Commissioners, in the previous draft  
15 these two items had been separate recommendations. The Commission requested that  
16 they be brought together since reapproaching someone who has previously dissented is  
17 not inappropriate if done in a sensitive way. And the language which I think was  
18 attempting to be faithful to your concern, Rhetaugh, is around page 127, lines 7 to 10.  
19 There have not been any public comments that describe how many times one would  
20 approach and would make it too much.

21 DR. DUMAS: I am very sensitive to this because I am in the process of  
22 reviewing some documents where there are questions about how often interviewers have  
23 approached people who are reluctant to agree to participate in a project and it is alleged  
24 that some interviewers have approached people as many as 14 times.

25 DR. SHAPIRO: I think that concern is entirely appropriate. However, I  
26 do think the language here, which I agree doesn't give us an upper limit like a number  
27 seven or a number three or something, but with appropriate care and sensitivity, I think  
28 that's pretty straightforward.

29 DR. DUMAS: The thing that bothers me is the care and sensitivity. I  
30 don't know what I would substitute for those words. I'm not suggesting that we ought  
31 to say how many times they should. But I think there should be some statement to the  
32 point that there is concern that beyond a certain level of contact or what have you people  
33 might feel coerced. I don't know exactly how to say that at this moment; I'll think more  
34 about that.

35 DR. SHAPIRO: Larry, then Eric.

1 DR. MIIKE: But I think that you've just explained the practical way you  
2 do it. You felt uncomfortable about it, and as an IRB member you would say it's not  
3 appropriate and sensitive to ask 14 times. I don't think we should be giving any guidance  
4 more specific than what we are.

5 DR. CASSELL: That has to be addressed and, of course, is the issue of  
6 are they going to pummel some poor person into saying yes again? So I don't think  
7 anything you say is going to change that. But care and sensitivity in regard to coercion,  
8 if you want to put the word "coercion" in there.

9 DR. SHAPIRO: Well, I think we all agree on the issue here, I don't think  
10 there's any disagreement amongst us. But Rhetaugh, if you could just think about that  
11 during the morning sometime and provide us with some language either to put in the  
12 recommendation, which you point out is already a little long, but perhaps it could be in  
13 the language below it, whichever you think is best. And if you could just provide us  
14 directly with that language, I think there's no disagreement amongst us on the issue.

15 DR. DUMAS: Okay.

16 PROF. CAPRON: Just to respond to one comment that Larry just made.  
17 I don't think there's any reason to believe that the IRB is going to be particularly aware  
18 of this. This would have to be advice that in effect governs the conduct of the  
19 researchers. Because I think what we're talking about is a situation which is below the  
20 level of visibility in all situations unless there is a companion to the researcher from the  
21 IRB walking around with the researcher any time he has contact with a subject.

22 I did have one other substantive question, which is the meaning of the  
23 phrase "at the point of notification." Jim or Eric, can you—

24 DR. SHAPIRO: That's in line 7?

25 PROF. CAPRON: Excuse me, in line 7, that's right.

26 DR. MESLIN: The notification will refer rather to recommendations  
27 regarding informing them or approaching them to participate. So it's the notification  
28 regarding participation. I think that's perhaps a little unclear.

29 DR. SHAPIRO: I agree with that.

30 PROF. CAPRON: And there's also the unique spelling of "incapable."

31 DR. SHAPIRO: Trying to save space. Leave out a few syllables here  
32 and there.

1 I think the idea here in my mind is straightforward; namely, the subject's  
2 refusal to participate or continue to participate at any time must be honored, period.  
3 And everything else is just commentary. Maybe that's the way we should— "A subject's  
4 refusal to participate or continue to participate in research must be honored." Then go  
5 on to say whatever it is we want. I think that was our sentiment here.

6 Any other comments regarding this? Thank you. Let's go on to  
7 Recommendation 4, which has to do with providing thorough justification, et cetera, and  
8 see what kind of comments.

9 Bernie?

10 DR. LO: Two comments. One, I was a little confused as to which of  
11 these recommendations were calls for regulatory change or guidance for IRBs. And this,  
12 in particular, it seems this and number 5 are really just restatements of what is already  
13 required in any research, whether it's on persons with mental disorders or not. So if we  
14 could somehow flag in the way these recommendations are worded which are the ones  
15 that require recommendations—

16 DR. CHILDRESS: These are all under, go back to 120,  
17 recommendations directed at the regulation of IRBs. That continues, as I understand  
18 what we've done, till we get to 147 where we offer additional guidance for IRBs. So as  
19 I understand the way this text has evolved, that's the distinction. So everything we're  
20 working with up to 147 would be a part of our recommendation for regulatory change.

21 MR. HOLTZMAN: Jim, I had the same confusion reading it before I saw  
22 that. It gets lost in the formatting, because right after you get that title you then say we  
23 will distinguish what we're talking about.

24 DR. CHILDRESS: I agree, I think there's confusion with that, too.

25 DR. SHAPIRO: If I could interrupt, I apologize, Jim. I think Bernie is  
26 raising what I think to be a substantive issue here; namely, if I could state it this way, it  
27 would just suggest that 4 and 5, however they get to be worded eventually, belong under  
28 "guidance" rather than here?

29 DR. LO: I guess my point is that I think right now any investigator is  
30 required to justify the research design they would use to the IRB and to provide a  
31 justification of why the benefit-to-risk ratio is acceptable to proceed with the research.

32 PROF. CAPRON: This goes beyond that. This says it not only must be  
33 acceptable, the risk side must be minimized. That's how I read it.

1 DR. LO: Isn't that in the current Federal regulations?

2 DR. MESLIN: Protections in the research—I'm sorry.

3 DR. SHAPIRO: Go ahead.

4 DR. MESLIN: I was going to say the Recommendation 4 is not explicitly  
5 in regulation now. There is no requirement that one provide to an IRB, requirement that  
6 one provide a justification in selection of a design, including those that you were  
7 describing at the top of 128. I think you're right by implication that as part of a protocol  
8 submission one provides a justification for what one is doing, including an assessment of  
9 risk and benefit, a description thereof. But I think, if I can recall the Commission's  
10 deliberations on this, it was to make explicit that, because of concerns about certain  
11 types of designs, investigators should be expected to provide justifications for those.

12 DR. SHAPIRO: Steve?

13 MR. HOLTZMAN: So is the issue one of wording again? I mean is the  
14 recommendation specifically directed to that set of types of protocols? And if so, should  
15 we get that up in the front of the sentence? "Provide a thorough justification of the  
16 research design involving..." that—

17 DR. MESLIN: It sounds like you just volunteered to write something.

18 DR. SHAPIRO: Well, the issue there I don't know that we should put in  
19 a recommendation. I'll have to think about it, Steve.

20 MR. HOLTZMAN: But which is it?

21 DR. SHAPIRO: I would prefer the broader definition, not the narrower  
22 definition. I think these are examples we have before us, there may be other examples,  
23 and I don't think there's any reason to draw a recommendation focused just on two or  
24 three research designs that happen to be controversial now. There might be others that  
25 come along. Diane?

26 DR. SCOTT-JONES: If we're really only putting them in as examples,  
27 then I guess I would have to go back to what Bernie said, researchers are already  
28 expected to do this. And I thought the point of this recommendation was to note that  
29 these designs at this time are especially controversial and might need special attention.

30 DR. SHAPIRO: Eric?

31 DR. CASSELL: What I want to emphasize—I wouldn't say they're

1 controversial, these are designs which may produce harm and they have been brought  
2 before us specifically and they're not going to go away.

3 DR. SHAPIRO: I think we all agree on that part of it. The question is  
4 whether we should draw the recommendation solely for those particular designs or as  
5 including those designs.

6 DR. CASSELL: "Including" is fine.

7 DR. SHAPIRO: That's my view also. And so we would meet our  
8 responsibilities regarding things that are brought before us and we believe need some  
9 attention.

10 MS. FLYNN: But we wouldn't preclude.

11 DR. SHAPIRO: We wouldn't preclude other things that may fall under  
12 this category sometime, that may indeed today fall under these categories, we just  
13 haven't focused on.

14 Any other comments? Arturo?

15 DR. BRITO: Yes, I have a comment about page 130, following this  
16 recommendation, the very last line where we talk about possible grounds for excluding  
17 subjects from particular studies. I think the language in number 3 there, "standard  
18 therapy is generally considered effective," needs to be a little bit stronger and more direct  
19 to where I think the standard therapy should be "is previously proven to be scientifically  
20 effective." The reason for that is I think it leaves too much room for interpretation there.

21 DR. SHAPIRO: That's a helpful suggestion. And other suggestions like  
22 that, please get them before us. But to the extent you can write them down, it's a very  
23 big help to us.

24 Trish?

25 MS. BACKLAR: Thank you. I think one could get into a problem with  
26 the words "standard therapy," for instance, with a disease like schizophrenia. One of the  
27 arguments going on now is what is standard therapy? So I have exactly the opposite  
28 reaction to that. And I don't mean to add to the problems, so I'll talk to you about it  
29 afterwards.

30 I did want to say that usually, on page 130, line 8, nowadays one would  
31 refer to this medication as anti-psychotic.

1 DR. SHAPIRO: Thank you.

2 Let's go on to Recommendation 5 which has to do with assessment of  
3 risks.

4 Laurie?

5 MS. FLYNN: I know this is contained somewhere in the text, but one of  
6 the things that we've talked about and I think there was broad agreement on is that we  
7 wanted, particularly in studies where we had some concerns about the vulnerability of  
8 the subject population or the potential benefit-risk ratio, we wanted to be sure there was  
9 linkage to community care for subjects who withdrew or who were dropped from the  
10 study. I think there's text about this somewhere in the document but it does not appear  
11 here. I would suggest that this is an important protection particularly given the concerns  
12 we've heard around relapse and the problems of some of these studies that have been laid  
13 before the Commission.

14 I would be interested in comments from Commissioners as to whether we  
15 might strengthen this in some way by adding a requirement that for this subject  
16 population, there be that obligation to assure that when they leave the study they are  
17 linked up to care in the community.

18 MS. BACKLAR: There's something about this on page 129, I think,  
19 following Recommendation 4. But it may not be enough and I don't know that it does  
20 actually say "aftercare."

21 MS.FLYNN: It's not very specific. I see it there and I think it's trying to  
22 reference—

23 MS. BACKLAR: Starting around line 10, it starts at 9 actually.

24 DR. CASSELL: But that's a wraparound provision. This is a broader  
25 provision than wraparound.

26 MS. FLYNN: I think some of the cases that we've heard about that were  
27 most troubling to us involved this very problem, that people left the research and were  
28 not connected. It is a critical problem if we accept up front that these are vulnerable  
29 folks and that they are going to be perhaps placed in greater potential vulnerability by  
30 virtue of being involved in the research. And when they leave the research, for whatever  
31 reason, it seems to me there's some obligation to assure a connection to care.

32 DR. SHAPIRO: I want to think about that a little more. I think I  
33 understand, Laurie, the point you're making. I want to be cautious about participating in

1 research entitling you to a whole series of benefits which no one else in the society has  
2 access to.

3 MS. FLYNN: Obviously, we can't assure that they're going to continue in  
4 the care, that the care is going to be good enough, all those things we can't know. But  
5 there would at least be an obligation to link them to the care providers in the community  
6 to make that connection, such as one makes when there is a discharge from a hospital.  
7 We don't just discharge people from a hospital and say "good luck." We discharge them  
8 from a hospital and we provide connection to their community care provider.

9 DR. SHAPIRO: Let's see how others feel about it.

10 Eric?

11 DR. MESLIN: I was just going to draw the Commission's attention to  
12 page 146, where it is further down the road than where you're referring to, Laurie, 146,  
13 lines 4 to 11, and specifically lines 8 to 11, "The research team must also make adequate  
14 provision for...." That may be where you were referring to elsewhere in the text.

15 MS. FLYNN: Yes.

16 DR. MESLIN: My understanding of Recommendation 5 was that it was  
17 still at the protocol review portion and that risks and benefits being described for the  
18 intervention itself rather than the risks of premature stopping and follow-up. But that's  
19 where it is also mentioned in the report. It can be moved, obviously.

20 DR. SHAPIRO: We'll certainly think about that further. And if you have  
21 any additional language that would be helpful to us, we'd be very happy to receive it. Go  
22 ahead, Trish.

23 MS. BACKLAR: When we were reviewing some of the protocols, Alex,  
24 remember we discussed this, Jim, in terms of the protocols that we were concerned  
25 about that people were not being provided with aftercare, and I had said something  
26 which you asked to be put into the text. And I can't remember precisely what it was but  
27 it was rather similar to what Laurie was bringing up.

28 DR. SHAPIRO: We will pursue that. Let's go on then to  
29 Recommendation 6. I'm sorry, Jim.

30 DR. CHILDRESS: On 6, I had some difficulties bringing our text  
31 together with our recommendation. And this may, in part, have to do with what Harold  
32 has already noted, that we really haven't spelled out what we expect to be involved in  
33 minimal risk research, what kind of assessment of competence and so forth would occur.

1 In terms of what Recommendation 6 itself states, I'm quite comfortable  
2 with that, as well as with number 7. But then when we try to explain what's involved,  
3 beginning at the bottom of 134, in both 6 and 7, it seems to me that we're introducing a  
4 second trigger for capacity assessment.

5 In our Recommendation 6, we're saying that for greater than minimal risk  
6 research we're presuming, and this is language that Alex and others worked out last time  
7 and I think it's very helpful, presuming an appropriate method and so forth, though a less  
8 formal method could be permitted if there are persuasive grounds for doing so. But then  
9 when we move on in the text, on 135, the first couple of lines and midway down, the  
10 other trigger has to do with when potential subjects are believed to be incapable of  
11 deciding. And believed by whom, under what circumstances and so forth, that triggers  
12 an assessment. Now it may be that we're thinking about that in relation to minimal risk.  
13 At any rate, we really do need to be clear as we try to explain this recommendation  
14 exactly what's going on, what will trigger what level of assessment of capacity.

15 DR. SHAPIRO: Alta, excuse me, I'm sorry I didn't see you.

16 PROF. CHARO: That's all right. Jim, I think that your concern can be  
17 addressed in a pretty straightforward way. If any person involved in enrolling a subject  
18 or working with a subject has reason to believe the subject has not got capacity to  
19 consent or to continually make decisions about whether or not to withdraw, at that  
20 moment an assessment should be made. And that is for all research and that's just the  
21 norm currently today as well.

22 In addition, at the moment at which an IRB is reviewing a protocol that  
23 involves greater than minimal risk research, it should look at the population to be  
24 studied. If it falls within these recommendations and if the research is greater than  
25 minimal risk, it should proceed on the assumption that capacity assessments will be  
26 needed unless the investigator can explain why they will not. So there are, in fact, two  
27 separate triggers.

28 DR. SHAPIRO: Alta, could I just ask a question? I'm just trying to make  
29 sure I understand what you've said, because if I do understand what you've said, it  
30 corresponds with my notion of what we were doing, although that's up for further  
31 discussion. That would mean that in minimal risk research, any time an investigator or  
32 anyone associated with the project feels there's some question about someone's capacity  
33 to look out for their own interests, that ought to trigger some kind of an assessment.  
34 That's in minimal risk research. And maybe we need to be clear about that, if that's what  
35 we believe, in the text.

36 However, this recommendation here deals with greater than minimal risk  
37 research where, if I understood what you said, the presumption is that an assessment



1 would be required unless, as you put it, this last sentence holds, I don't want to repeat it.  
2 Is that consistent with what you said?

3 PROF. CHARO: Yes. The only clarification I'd make is that these are not  
4 mutually exclusive categories. Perhaps the easiest thing is to think about them  
5 chronologically. The protocol first comes to the IRB. If it's minimal risk and the IRB  
6 thinks that these people are not going to have capacity to consent, they may require a  
7 competency assessment or not. That's their usual job. If it's greater than minimal risk,  
8 we ask that they assume you're going to need it unless shown otherwise. That's the first  
9 step of the chronology.

10 The second step is, regardless of the level of risk and regardless of the  
11 IRB's actions, at any point along the way in the actual implementation of the research, if  
12 an investigator or somebody enrolling the person or another person working with the  
13 subject says I think this person has lost their capacity to be an effective partner in the  
14 research, we need to stop and make an assessment here about this person's capabilities.

15 DR. SHAPIRO: Other comments?

16 Laurie?

17 MS. FLYNN: I just want to understand this one because I certainly  
18 generally support the thrust of it. I believe we've determined that greater than minimal  
19 risk research would include most, if not all, clinical trials of new medications. Would  
20 this then mean that people who are showing up to participate in a clinical trial for a new  
21 anxiety medication, people who are not likely to be by definition folks who would  
22 necessarily have their competency questioned, would now be subjected to this kind of  
23 thing? That this would be an assumption being made that—

24 DR. SHAPIRO: If I understand it, Laurie, just to try to answer your  
25 question directly, tell me if I've misunderstood, Alta, is that at the IRB approval level  
26 when it is initially approved, if the IRB feels that this is a population for which this  
27 problem doesn't arise, then they can waive that requirement. If they feel this is a  
28 population where that's an open issue, then they may not waive the requirement. But the  
29 IRB could make that decision. That's the purpose, as I understand it, of lines 6 through  
30 8 of Recommendation 6.

31 Bernie?

32 DR. LO: Let me inject another issue here with regard to  
33 Recommendation 6, which is the requirement that the capacity assessment be done by  
34 someone independent of the research team qualified in an appropriate manner. It seems  
35 to me in a lot of situations, particularly for minimal risk research, many protocols will try

1 to meet this requirement by saying we will go to the personal physician of the patient  
2 who is not a member of our research team and ask that personal physician whether the  
3 potential subject has capacity or not. One question is often those are not very formal  
4 assessments and it seems to me it would be unusual for the personal doctor to then say,  
5 okay, come into my office, schedule a 20-minute appointment, let's go through a  
6 standard protocol to determine the person's capacity. Are we comfortable with the  
7 doctor just saying let me think about that, yes, I think this person does have capacity, or  
8 are we really requiring a much more formalized assessment?

9 Secondly, I would like to see in the accompanying text some justification,  
10 which I didn't find in this section, for having the person be independent of the research  
11 team. I think it's elsewhere in the report. I think we need to acknowledge that this will  
12 be a substantial change in the way the protocol is run and could be a substantial burden  
13 on some studies to have someone, presumably they would have to be—I'm not sure how  
14 this would be done and I think there are real practical issues of is this going to be  
15 covered in the cost of doing the study—having an outside person independent of the  
16 team conduct a capacity assessment? If I weren't sure, I would not want to pay for a  
17 separate office visit to determine one's capacity to consent to a research.

18 So I think there are a lot of issues here that we at least need to  
19 acknowledge. My sense is that many researchers feel that this recommendation will shut  
20 off a lot of research.

21 DR. SHAPIRO: Eric?

22 DR. CASSELL: Well, the recommendation requires the employment of  
23 an appropriate method. It doesn't just say a qualified professional can just say he is or  
24 she is, so forth; it requires a methodology. The methodology should be specified and the  
25 IRB should cover that. But, yes, this is going to be a substantial burden for people doing  
26 this kind of research. But it also prevents probably the central abuse, that the  
27 investigator who has an interest in going ahead also does the assessment of capacity.  
28 That's how we got into this in the first place.

29 So I think we just have to accept the fact that this particular issue is one  
30 that's going to be a problem for investigators, and rightly so, because these are people  
31 who have an interest in the research going forward that may preclude their doing the best  
32 assessment possible. We just know that. And you want that spelled out in it that there's  
33 a "double agent" problem here, then that might be necessary to spell that out. But I  
34 personally don't think it is necessary to spell that out.

35 DR. SHAPIRO: Rhetaugh?

36 DR. DUMAS: I'd just like to point out that this is one of the areas where

1 some of my colleagues in the psychiatric field are taking exception to the idea that  
2 someone other than a member of the research team would be involved in making that  
3 decision.

4 DR. SHAPIRO: Alta?

5 PROF. CHARO: I'd like to speak in support of the current approach here.  
6 My experience working with health care professionals in several institutions has been  
7 that competency is only questioned, in that large gray zone, competency is only  
8 questioned when people want to do something that the health care professional  
9 disapproves of. When people want to do what the doctor or the nurse or the other  
10 professional wants them to do, rarely in these ambiguous cases do people stop and say,  
11 gee, I wonder if this person can really consent?

12 DR. LO: That's absolutely right.

13 PROF. CHARO: And the disagreement or unwillingness or obstinacy is  
14 usually used as the first sign the person is probably incompetent because they're not  
15 going along with the recommended course of action. And I truly, truly, truly do not  
16 believe that this is motivated by evil intentions. I think it is genuinely motivated by  
17 people who are embedded in a situation in which they're trying to do what they think is  
18 right and they look at somebody who seems to be making decisions that are all wrong  
19 and there's got to be an explanation. And it's going to be a lack of competency.

20 I find it hard to believe that some of that same dynamic does not exist as  
21 well in the research context. Which is why I think that in those circumstances, where  
22 you genuinely need to make this assessment in a serious fashion, that the independence  
23 of the assessor is very valuable because it removes some of that embedded context  
24 problem that I've seen so frequently.

25 DR. SHAPIRO: Laurie?

26 MS. FLYNN: I want to endorse this recommendation strongly. Again,  
27 this recommendation is very, very similar language to policy we adopted in my  
28 organization in 1995 for precisely the reason that Eric points out, that this is a very  
29 appropriate safeguard, it will be a burden in the research arena, but it's an appropriate  
30 way to make certain that as people enter studies we know that they have had an  
31 independent assessment. So we feel strongly that this is an important protection and,  
32 although it is indeed a burden, that it can be handled and should be seen as part of the  
33 price that one pays in a research institution for the privilege of doing research with these  
34 individuals.

35 DR. SHAPIRO: Bernie?

1 DR. LO: I think if we're going to keep this independent requirement, I  
2 would want us to make a recommendation somewhere that NIH and other funders of  
3 research need to write that in as part of the legitimate cost of doing the research.

4 DR. SHAPIRO: I think we will get in the final report some general  
5 comments about it. This is not the only place where that comes up. It comes up in a lot  
6 of places, virtually everywhere where we're asking for additional efforts.

7 Alex?

8 PROF. CAPRON: I agree with Alta's observation. I want to add,  
9 however, that the review of the protocols that we engaged in, indicated the need for  
10 exactly this kind of a recommendation, because in none of those protocols that we  
11 reviewed was there any indication of any attempt to assess the capacity of subjects, some  
12 of whom were enrolled precisely because they had major disorders, and all of the  
13 protocols we were looking at were ones in which their published descriptions involved  
14 more than minimal risk.

15 I think this is one of those recommendations which may be onerous but is  
16 not something that comes out of the blue. It is based upon experience in this field.

17 DR. SHAPIRO: Okay. If I could just make a recommendation. I think  
18 that the Commission probably is in support of this. We will have to write our  
19 recommendations regarding minimal risk which relates to assessment in that case, and  
20 that will have to come before us and that will give us a chance to look at it altogether  
21 when we do look at that. And we'll have to clarify, Jim, the language that you pointed to  
22 on page 135, if I remember correctly. So we will certainly do that. But I think there is  
23 broad support for this. But we will need to clarify and bring together our  
24 recommendations regarding minimal risk.

25 PROF. CAPRON: Mr. Chairman, there are two points in the commentary  
26 that seem confusing to me. The first occurs on page 135 at line 1, the statement carrying  
27 over from the previous page is "the capacity assessment should only be required," et  
28 cetera, et cetera.

29 DR. SHAPIRO: That does have to be clarified. I agree with you.

30 PROF. CAPRON: Okay. And I have a suggestion there.

31 The other is on the top of page 136, the justification that is given for  
32 value of this capacity assessment is that, by finding the subject incapable, investigators  
33 would then be obligated to approach a third party to make a decision on behalf of the  
34 person. It seems to me that that obliges the real value, which is that people will not be

1 enrolled in research until a person who is capable of making a judgment about their  
2 participation is called upon to make that judgement. And I'll give you language because  
3 it doesn't seem, if people agree with that, it doesn't spell out really the justification very  
4 well.

5 DR. CHILDRESS: I think you're quite right. I'd actually changed it in  
6 my text. I assume that rather than value we probably meant the effect; that is, it  
7 describes an effect rather than—

8 PROF. CAPRON: I think it would be fine to describe the value of it.

9 DR. CHILDRESS: Right. But we would need something very different  
10 from this. I agree with your suggestion.

11 DR. SHAPIRO: Alex, can you give us language on both of those  
12 because both of those need some language.

13 PROF. CAPRON: Do you want me to read a sentence and see if it works,  
14 just very quickly?

15 DR. SHAPIRO: Why don't we do that since we there right now.

16 PROF. CAPRON: "Capacity assessment," this is the thing on the top of  
17 135, "Capacity assessments are usually required only when there are reasons to believe  
18 potential subjects may be incapable of deciding about their participation." And then as  
19 we work down from there, we get to the point we say, "Our presumption is that for  
20 studies involving greater than minimal risk IRBs will always expect..." So it changes the  
21 first to descriptive and then goes from there. Is that satisfactory?

22 DR. SHAPIRO: That's helpful. Thank you.

23 Let's go on then to Recommendation 7.

24 DR. CASSELL: Just to clarify that. That leaves that sentence, "Our  
25 presumption is that for studies involving..." that stays in?

26 PROF. CAPRON: Sure. No change at all there.

27 DR. CHILDRESS: Yes, no change in that.

28 DR. CASSELL: So it isn't a question of, it's that circular thing that says if  
29 you don't think they have capacity, you have to measure their capacity.

1 PROF. CAPRON: No.

2 DR. SHAPIRO: Thank you.

3 Recommendation 7 is what I call the notification recommendation. Any  
4 comments regarding that particular recommendation?

5 DR. MURRAY: I have a comment in the text that follows.

6 DR. SHAPIRO: That was just the text we were working on. Do you  
7 want to make the comment now?

8 DR. MURRAY: Yes.

9 DR. SHAPIRO: Fine. Go ahead.

10 DR. MURRAY: Lines end of 12 through 15, that statement. The current  
11 sentence reads, "Studies involving non-invasive interventions which satisfy the conditions  
12 of minimal risk defined in the Common Rule," et cetera, "would probably not result in  
13 IRBs expecting such an assessment to occur." Now I can't tell if we are giving a simple  
14 description there and we're going to build an argument from that, or if we are actually  
15 prescribing to IRBs that they ought not to expect such an assessment to occur. It's just I  
16 found that ambiguous and I'd just like to be clear which it is we're saying. Is it  
17 descriptive or prescriptive?

18 DR. SHAPIRO: Eric?

19 DR. MESLIN: It was attempting to be a statement that shows that the  
20 presumption would not be in favor of requiring this in all instances because the  
21 assumption is that a capacity assessment would not be needed.

22 PROF. CAPRON: I move to strike that sentence.

23 DR. SHAPIRO: It doesn't add a lot. I agree with that.

24 DR. CHILDRESS: I agree. This is another indication of why we need to  
25 state, as Harold suggested, exactly what we expect to go on in the area of minimal risk  
26 research.

27 PROF. CAPRON: And part of the reason that I move to strike it, just to  
28 be clear, is there is no necessary connection at all between minimal risk and more than  
29 minimal risk as to this assessment issue. You don't want to enroll incapable subjects in  
30 either case. It's just that the probable harm is less when you make a mistake in one case

1 than in the other. And so I think that leaving that sentence out doesn't put us on the side  
2 of seeming to suggest that the two are linked.

3 DR. SHAPIRO: Steve?

4 MR. HOLTZMAN: I'm just wondering if some ambiguity doesn't arise  
5 here from the word "assessment." Are we referring to assessment, per se, or to the  
6 formal process of assessment being recommended? Alta's comments about assessing,  
7 that you never enroll someone that you feel incapable of assessing, I agree, regardless of  
8 the minimal risk.

9 DR. SHAPIRO: Let me suggest, I think that really we do need, in order  
10 to really resolve this carefully, we do need to have our recommendations regarding  
11 minimal risk and I think it will be easier to do the language here. I really do sense an  
12 agreement amongst us on this, but we'll have to get the language and make sure that  
13 that's correct. We will try to do that part before we leave here today.

14 Let me ask a question then about Recommendation 7, which is the  
15 notification, as I said before, any comments regarding that? Okay. Eric, there are two  
16 issues, before we continue on with the recommendations, there are two issues I think it  
17 might be useful to interject now and then we can take a break and take a stretch or  
18 something and then go on with some of the other recommendations. One is minimal  
19 risk. We've already talked about that. Do you want to say anything further, or we'll just  
20 go to the drafting board? We might take a break which will give us a chance to draft  
21 some material here.

22 DR. MESLIN: I'd only like to point out an issue that has arisen in the  
23 public comments that we received that are reflected in the flow chart in appendix 3 but  
24 are not reflected explicitly in the text since we do not have a recommendation relating to  
25 minimal risk. That comment referred to the assumption that IRBs can utilize a waiver of  
26 informed consent; they can waive informed consent in minimal risk research if the  
27 conditions within the Common Rule have been satisfied. There's no difference for  
28 minimal risk research, so goes the argument. Now we have had this implied in the text  
29 but it has never been made explicit.

30 Two points follow from that. If the Commission agrees that that is  
31 appropriate, because by implication you've been saying it all along, then I would suggest  
32 that that explicitly be created in the text. And secondly, it would be very useful if a  
33 single recommendation regarding minimal risk were constructed that included both that  
34 provision as well as provisions regarding assent and dissent, how those are acceptable  
35 and when they are not, and the capacity assessment issue which we've just described.

36 So I raise those for you. I think the first is noncontroversial, but I wanted

1 to make sure that you were aware that there have been public comments on this. In fact,  
2 at the last meeting in Alexandria there was a public statement asking the Commission  
3 whether we would, in fact, be making that clear. It's not explicit in the text but is  
4 implied.

5 DR. SHAPIRO: So is there any—I don't see how there could be any  
6 objection to drafting a proposal, so I don't want to ask that question. But I think that's a  
7 proposal we perhaps could draft relatively quickly because I think it's straightforward.  
8 Then we could see whether you found it straightforward when you looked at it or not.  
9 So I'm going to propose that when we break in a few minutes that we'll assign two or  
10 three of us to actually draft that proposal and present us something on that later on this  
11 morning.

12 Let's now also take up the issue which I flagged before when I was  
13 making my introductory remarks regarding health care professionals. Let me see where  
14 it is dealt with first. If I remember, it's page 86 where we make certain statements. I'm  
15 going to turn to Eric to just describe the issues as I see them. It's really all at page 86,  
16 forgetting the lines 5 through 16 or something which really refers to someone else's  
17 views of this matter.

18 Eric, why don't I turn to you because I do think we need to have some  
19 discussion and resolve where we stand on this issue.

20 DR. MESLIN: I'll just briefly remind the Commissioners, it turns out that  
21 we begin the discussion on line 6 of page 85 where the discussion of independent  
22 professional support for subjects and surrogates begins. It continues from that page all  
23 the way up to line 4 of 86. And then there is a continuation of that discussion in the  
24 guidance section of the report on page 151. All that is said on 151, and as you turn to it  
25 you'll see it yourself, is that IRBs may wish to consider recommending that an  
26 independent clinician be available to counsel the subjects, a responsible health care  
27 professional.

28 There is, in short, a confusion about the number of individuals who we  
29 are calling health care professionals and what their roles and responsibilities are. My  
30 understanding in relating to you what the public comments have said...are first, it would  
31 be excessively burdensome to require that every person who participates in research  
32 must always have available to them a health care professional to counsel them, plus or  
33 minus counsel of their legally authorized representative. That's one issue. The second  
34 issue is whether, in cases of greater than minimal risk research, without the prospect of  
35 direct medical benefits to the subject, where the subjects might be incapable—I  
36 apologize for the three parts of that recommendation. You are currently describing the  
37 role of the legally authorized representative as allowing patients to continue or  
38 withdrawing them, but not to enroll them. And here, the role of the health care



1 professional would rear his or her head. Is it required that when the legally authorized  
2 representative decides part way through a study, that it would be appropriate to  
3 withdraw someone, that they could do that only upon consultation with a health care  
4 professional, or is it simply that someone should be available should they seek to obtain  
5 that counsel? It is a very simple problem that I believe the text has confused.

6 DR. SHAPIRO: I think that we might focus on the issue of when they are  
7 required, because obviously anyone could always make use of it and so on. But it would  
8 be required when a patient lacked capacity to decide and so, no. So the real issue is—I'm  
9 somewhat confused myself as to how the Commission feels about this. That is, when you  
10 feel this extra assistance is required as opposed to when it should be considered. I would  
11 just like some help on what the Commission is thinking on this issue. Eric?

12 DR. CASSELL: Well, I think that if we required it for everybody, or  
13 really put a requirement in, that is very burdensome. On the other hand, it ought to be  
14 mandated that a research team understands that the legally authorized representative or  
15 the patient can request such a person. They can request it under any circumstance, but  
16 it's not required under any circumstance. When there is risk, regular to minimal risk, I  
17 think whether there's benefit or not, there should be an identified health care professional  
18 out there.

19 DR. SHAPIRO: Well, in that case Eric—I'm just trying to clear it up in  
20 my mind what your thinking is. In that case, if it's greater than minimal risk and they  
21 know there's a health care professional available if they want, must they use them?

22 DR. CASSELL: No, I don't think you must use anything.

23 DR. SHAPIRO: I'm just asking.

24 DR. CASSELL: No, I think it should be available, but they do not have  
25 to use them.

26 DR. SHAPIRO: So the distinction you've drawn, if I understand it  
27 correctly again—I apologize if I'm repeating myself—and that is unless the minimal risk  
28 research patients and/or other representatives, I don't understand, that they may request  
29 that.

30 DR. CASSELL: Yes.

31 DR. SHAPRIO: And in greater than minimal risk research, they need to  
32 be informed that someone is available if they want it.

33 DR. CASSELL: Yes.

1 DR. SHAPIRO: That's your view. Let's just see how that feels to the rest  
2 of the Commission. Thank you very much. How do other Commissioners feel about  
3 that? Bernie?

4 DR. LO: Let me follow up with the greater than minimal risk. Someone  
5 ought to be designated as being available. Could that person be the personal physician of  
6 the patient? Because there's language at some point saying that you had to have another  
7 professional advising the health care professional.

8 DR. CASSELL That's the team approach.

9 DR. LO: So what you're saying, Eric, is that the patient should be notified  
10 that either their personal physician or so and so who has been formally invited by the  
11 study to serve in this role is available to them.

12 DR. CASSELL: And we don't require yet another specialist to advise the  
13 sub-specialist and so forth.

14 DR. SHAPIRO: Let me just ask the obvious question here so just I can  
15 be clear in my mind. What if the personal physician is the investigator on this subject? I  
16 just want to make sure I understand.

17 PROF. CAPRON: And don't we need to, again, vis-a-vis Bernie's  
18 comments about research grants being made adequate to fund our proposal, be clear that  
19 available means paid for by someone? Because it may not be regarded as reimbursable  
20 treatment cost.

21 DR. LO: Now let me ask the next question. There are some protocols  
22 that are much riskier than others, such as symptom provocation, withdrawal patients,  
23 randomizing where there's a known effective. What we want to throw out is in that  
24 situation, do you want to have a mandatory discussion with an advisor as opposed to  
25 making him available. The issue is that they really are on different levels of benefits or  
26 risk involved.

27 DR. LO: Let's follow it through. Let's suppose we mandated it. And the  
28 subject comes through and says "I don't care what my advisor ..."—and we get into that  
29 kind of ... I think people have to have a choice in this. If they have the capacity to  
30 consent....

31 DR. SHAPIRO: My own thought on that, and I think that's right and I  
32 think there are other kinds of studies we can suggest which are even riskier and so on  
33 and the IRB always has options to make requests. I think that I'm satisfied here that they  
34 must perform if something is available. As a subject is competent or incompetent, we

1 have to rely on competency somewhere along the line here or this whole thing sort of  
2 doesn't add up. I would be satisfied, just speaking to myself now—the way that Eric  
3 phrased it, although we need to get language together so we can look at it. All right. We  
4 will try to draft some language on the health care professional consistent with this kind  
5 of approach. I would like to suggest, we've gone for about an hour and a half now. I  
6 would like to suggest that we take a break, but I'm going to make some arbitrary  
7 announcements here regarding drafting material. And Eric, I wonder if you and Alta and  
8 anyone else who wants to participate, providing there are not more than two  
9 others—can draft something on the minimal risk side. The other thing that I think we  
10 have to do is clarify just what we want to do along the lines of the talk about the health  
11 care professionals. And Jim, I was going to ask you if you and Eric can get together with  
12 anyone else who might want to participate and we could try to get back here by 10:00,  
13 which will give us a half hour of drafting time and let's see what we have. Is that  
14 acceptable? Thank you very much. We're recessed for half an hour.

15 DR. SHAPIRO: I'd like to return to some subjects we raised earlier and  
16 ask our colleagues if they drafted some language that we could at least consider. We  
17 will, of course, incorporate this into the document as appropriate. Let me first go to Eric,  
18 who was working with a group. If you recall, this had to do the role of the health care  
19 professional, just to say it in summary form. Eric?

20 DR. CASSELL: There are two clauses. The first clause is for any  
21 research subjects or their legally authorized representatives to be informed that they may  
22 request the opinion of an independent health care professional about their participation in  
23 their research. Investigators must make available any information or access to the subject  
24 or research site that the independent health care professional requests in relationship to  
25 the investigation. Clause two. For greater than minimal risk research, whether or not  
26 benefit is anticipated, an independent health care professional must be identified in  
27 advance of the start of the research. The subjects or their legally authorized  
28 representatives may or may not request the opinion of the independent health care  
29 professional if they wish. The investigators must make available any information or  
30 aspect of the patient or research that the independent health care professional requests.  
31 Thank you. These are comments.

32 DR. CHILDRESS: I think one of the big questions that emerges out of  
33 the first question is that for regulation, really guidance for our IRBs takes on quite a  
34 different tone.

35 PROF. CAPRON: Certainly the funding issue.

36 DR. SHAPIRO: Quite aside from the funding issue, it's a different kind of  
37 issue which we can come back to. The issue as I understand it is whether or not we think  
38 that Eric has captured the intent of our discussion, namely to try just feed it back. There

1 are two aspects of your recommendation. One is the fact that if the patient or subject  
2 and/or their legally authorized representatives requests the use of the health care  
3 professional for advice or assistance, then investigators must yield the appropriate  
4 information—must be informed. You've said it explicitly, but I don't know what it would  
5 mean if that weren't the case, if they only got some of the information. So that seems to  
6 me—I just highlight it because it wasn't mentioned before, but it seems very  
7 straightforward to me. So that part of it seems straightforward. Now with the issue of  
8 minimal risk research, they may request the use of someone.

9 DR. CASSELL: But we don't have to identify in advance.

10 DR. SHAPIRO: That's right. And they may not. That's just something  
11 that the patient or their legally authorized representative does: request it, it has to be  
12 provided. In greater than minimal risk research, they must identify someone and patients  
13 and/or their legally authorized representative may request. Just so I understand. Do  
14 people have any concerns? I'll come back to the issue of where it goes in the report in a  
15 moment. Yes, Bernie?

16 DR. LO: I have two suggested modifications. One when you say  
17 independent health care professional. At least once I'd like to suggest we change it to be  
18 "health care professional independent of the research team." Because independence to  
19 some may mean independent of the institution or hospital.

20 DR. CASSELL: I actually was going to say be the super, because we  
21 have a whole set of paragraphs about independent professional support.

22 DR. LO: And then I didn't quite catch the sentences about what  
23 information must be provided. It seems to me that what you would want is information  
24 about the protocol, the risks and benefits. But if that person would say "well, show me  
25 your preliminary results, I want to see them." It seems to me that would not be  
26 legitimate.

27 DR. CASSELL: I don't have that in here. I have "to the subject or  
28 research site, subject protocol or research site."

29 DR. LO: So the information is about the protocol, the research. I didn't  
30 understand.

31 PROF. CAPRON: Do you think it is illegitimate, Bernie, for a subject to  
32 say "show me your preliminary results?"

33 DR. LO: I think they may ask, but I think it may be part of the design  
34 where there's blinding and there's concern about taking preliminary looks. If that's part of

1 the protocol and explained as such—the subject may ask and they may be dissatisfied  
2 with the explanation, but I don't think there should be any obligation on the researcher to  
3 disclose preliminary information which would undermine the research program.

4 PROF. CAPRON: But obviously, anything that a research subject would  
5 have access to would be available to the advisor.

6 DR. SHAPIRO: I actually think that's a neat and summary way to put it.  
7 And so if the protocol didn't allow the subject to access it, then of course others couldn't  
8 have access. Okay. I think you've captured—

9 PROF. CAPRON: Could I ask one other question? Back on page 87,  
10 which is where the descriptive part in chapter 3 about this independent professional  
11 comes in. At the end of line 4 or following line 4, I wonder if it would be desirable there  
12 to tie together the notion that the person who we say had been previously acquainted  
13 with the potential subject would therefore potentially be the person who was their treater  
14 previously. If we had language of this sort in another sentence, when as is usually  
15 desirable, the researcher is not the health care professional who has been providing  
16 services to the subject as patient, this independent advice can come from that person. In  
17 other words, tying the two thoughts together that we've talked about. The advisability  
18 that we not have as a routine matter physicians and others caring for patients turn around  
19 and ask them to be subjects. And the fact that we're saying that there should be an  
20 independent person and all the better if he knows the subject. Would a sentence of that  
21 sort be acceptable there?

22 DR. SHAPIRO: Is the idea—I just want to make sure I understand what  
23 you're getting it—is the idea being that when someone who is serving as the caregiver in  
24 this case, the physician in this case for this person, if they are not involved with research,  
25 they would ideal for this kind of position.

26 PROF. CAPRON: We already say that in each instance. And so this is  
27 just tying that thought back to our previous thoughts about the desirability of not having  
28 the caregiver turn around and becoming the researcher.

29 MS. FLYNN: Isn't that captured on page 85, lines 13, 14, 15, 16, right in  
30 there? Don't we say it right in there? I'm not sure why we need to say it again.

31 PROF. CAPRON: No, I don't think it is. This refers to an independent  
32 and properly skilled person available to be the advisor. We then go and say "in each  
33 instance, this advisor should, whenever possible, have been previously acquainted with  
34 the potential subject." And I'm just trying to close the circle and tie it into our previous  
35 recommendation and say "when, as is usually desirable, the researcher is not the health  
36 care professional who has taken care of the patient previously." That person would be

1 the ideal person to play this role of independent advisor, to take on the role of  
2 independent advisor. Or that person is available to play this role.

3 DR. SHAPIRO: I think I agree with you, but I'd like you to write out the  
4 sentence and I'd like to look at it. I think it actually may be helpful. It doesn't introduce  
5 anything new, any new idea, but it might be helpful. And so if you can just do that, I  
6 would appreciate it. Okay. We will have to deal with where this discussion regarding  
7 health care professional comes in now. Currently it's only in under "Guidance." And if I  
8 understand the recommendation here, it's not really guidance we're asking for here, we're  
9 asking for changes in behavior. I don't know exactly where it will go, but it will have to  
10 find its way into that list. We'll work that out. Okay. Let's go on now. There's another  
11 group that was looking at the issue of minimal risk. Let me turn to Eric. This is a  
12 question, just to remind everybody, of wanting to state what is consistent with our  
13 ongoing text here, what our views are on minimal risk research. And that also will have  
14 to find its way to the appropriate spot.

15 DR. MESLIN: I'm reading what Alta Charo has principally drafted with  
16 some modification; It's in two parts. First, research that presents minimal risk, whether or  
17 not it offers the prospect of direct medical benefit to the subject—this is the italicized  
18 version—the recommendation reads as follows. An IRB may approve protocols in this  
19 category if a) the potential subject consents or b) the potential subject's legally  
20 authorized representative gives—and I'm going to edit on the fly if you don't  
21 mind—authorizes or gives permission, since we have agreed that third parties cannot  
22 consent directly. Additionally, when the legally authorized representative gives this  
23 permission, a subject's assent should be sought and, of course, dissent would need to be  
24 honored as well. That's working language. There is a second part to this  
25 recommendation, which is that nothing in these recommendations is intended to limit the  
26 use of current regulations to approve expedited IRB review and waivers of the usual  
27 consent requirement. I know that Alex may have had some comments on this. My only  
28 point would be that we have mentioned assent and dissent in this recommendation  
29 because we have described it in the text earlier in the report and we have attempted to  
30 make clear what the public comment was requesting. And we've already indicated this in  
31 a flow chart about consent waivers.

32 DR. SHAPIRO: Comments, questions regarding this? Jim?

33 DR. CHILDRESS: I just have one question. Even though we talk about  
34 assent as well as dissent in the text, we don't really anywhere in the recommendations  
35 bring in a fuller notion of assent. It seems to me if we do that, then we're going to need  
36 to amplify things quite a bit more. And that's not necessarily to argue against it, it's just  
37 that we've taken the notion of dissent to allow the opting out under any circumstances.  
38 And if you want to make a stronger role for assent, then I think we'll probably have to go  
39 back and rework some of this.

1                   PROF. CAPRON: In a way, to second what Jim says, I think if the point  
2 is to develop a recommendation around assent, then that makes sense to me. If the  
3 language that you read is not further elaborated, it seems to me that it is more  
4 appropriate as commentary around Recommendations 8 and 9. The thought being that  
5 we introduce this whole section on page 121, I guess or 122-120, excuse me—by saying  
6 that these are recommendations for regulatory reform. And the language of what you are  
7 saying here, particularly the language about nothing here is intended to alter the usual  
8 rules, none of what's there really sounds to me as though it's intended to alter the usual  
9 rules around minimal risk. And I think as a matter of logic, we ought to explain what our  
10 view is on the minimal risk or less research and then say that with research of more than  
11 minimal risk, that we are recommending changes in regulatory reform. Rather than trying  
12 now to craft language that rises to the level of a recommendation, where I think the need  
13 for precision certainly greater than if it's merely commentary. So I would favor. Now if  
14 you come up with some language which you believe would involve a real notion of  
15 assent which is different than the present regulations provide for, then obviously such a  
16 recommendation should come before us as a recommendation.

17                   DR. MESLIN: I'd just like to make an observation. On page 60, there is a  
18 short paragraph that I think the Chair agrees requires some more careful rewording. This  
19 is a paragraph that describes what the national commissions use on assent and dissent  
20 work. I'm taking from what you said, Alex, that by moving in the direction away from it  
21 being a recommendation as a commentary, that it might be appropriate both in the text of  
22 page 60 to amplify that issue and then, if necessary, somewhere around 120—around  
23 recommendation 8 on 130, somewhere around 134. That would be some other  
24 commentary, prior to the greater than minimal risk section.

25                   DR. SHAPIRO: I think the notion that we have to say what it is we  
26 support with respect to minimal risk, it ought to come first rather than an afterthought to  
27 this. I think it does make sense. And I also think—I've forgotten the page number  
28 now—but where we do discuss assent and dissent, we don't make anything of it in the  
29 report currently there. We don't know why this is discussed or why it's in there, and it  
30 does relate at the end to deciding whether assent is sufficient in some cases to go ahead  
31 and enroll people. And that we deal with directly here. So we just have to beef up that  
32 explanation, why it is we're raising these issues. But I think other than that, this seems to  
33 me something that we can put in our next draft. Any other comments, questions? Okay.  
34 Let's go back. I want to thank all those who did some drafting in the interim and let's go  
35 back to considering some of the recommendations that we have before us and what our  
36 views and so on are. Now we can go to Recommendations 8 and 9. I think the  
37 recommendations that we are about to go through now, 8, 9, 10, 11 and then 12 and 13  
38 are where, of the ones that we haven't dealt with so far today, are the ones that have  
39 generated the most comment and reactions. So we ought to take care as we go through  
40 these. We have recommendations, I think we can take Recommendations 8, and 9  
41 together. This is now dealing with research that presents greater than minimal risk and

1 offers the prospect of direct medical benefit to the subject. In the recommendation itself,  
2 8 I think, is relatively straightforward. It simply says that informed consent, that's what is  
3 required and I think it's self-explanatory. Nine, of course, deals with a case of potential  
4 subjects who are currently incapable of making decisions. I would just make two  
5 comments and then we can just turn to see what further discussions there are. Maybe I'll  
6 turn to Eric, also to see what some of the public comments on this have been. My own  
7 view currently on 9—I won't have anything further to say about 8—I really have two  
8 views. One, I think c)—this ought to be broken up into two different—you ought to  
9 have c) and d) rather than c). C) attempts to get two different ideas across in one  
10 sentence and it makes more sense to try to try to break it into two. That's a relatively  
11 small issue, no substantive issue there. And under a) and b) under 9, under a), you go  
12 talk about expressed willingness to participate. And my own view, participation in  
13 research is, I think what the intent was, in this type of research as opposed to research  
14 overall. But we can come back and discuss that in a few moments. But Eric, do you want  
15 to talk about the public comments? You can't characterize them all, obviously—we don't  
16 have time. But what do you think some of the highlights are?

17 DR. MESLIN: I think the only thing that has come up may have been  
18 confusion on the part of some of the public comments that took the Commission to be  
19 saying that the research that offers the prospect of direct medical benefit, even if it has a  
20 greater than minimal risk threshold, that we would be imposing a strict standard of  
21 advance consent. Some kind of documentation of that advance consent and a  
22 burdensome requirement with respect to legally authorized representatives. I don't think  
23 that that's what Recommendation 9 is saying. I think it is saying that for research that  
24 involves the prospect of direct benefit, these are the ways it can occur and it provides  
25 ample opportunity for that to go forward. Not much more to add to that.

26 MS. BACKLAR: Then how would you know that somebody had  
27 expressed their willingness to participate if you don't have some documentation of some  
28 sort? I'm asking.

29 PROF. CHARO: I think we are walking the same kind of fine line here  
30 that we do in a clinical context where family members—that's most typically what we're  
31 talking about here, because we have excluded from this institutional representatives,  
32 right? We walk a fine line where family members make decisions on behalf of people  
33 who have lost capacity to make decisions for themselves. And we have chosen on the  
34 clinical context not to limit family members to making decision that have been previously  
35 documented in writing. We give them far more leeway. And the question has been  
36 whether we should mimic that degree of leeway here, or whether we should narrow it  
37 specifically because it's a research context. Now because this research, although not at  
38 the same level of certainty and benefit as standard therapy frequently is, is nonetheless  
39 research that offers the prospect of benefit. I understood us to be trying to parallel the  
40 rules for clinical decisionmaking and basically placing a fair amount of trust in the



1 representatives, typically family members, who are making decisions in this context. I  
2 appreciate that in the context of research without benefit, the equation might be a little  
3 bit different. The degree of decisionmaking authority one might want to grant is  
4 different. But I understood this to be one that was paralleling clinical decisionmaking  
5 privileges by family members. That we understand that we've relied on that language in  
6 this particular instance. Because I think it raises a problem of why is it adequate in one  
7 place and not in the other, and that is the discretion of the family based on their  
8 knowledge of the person and informal as opposed to unsubstantiated willingness or  
9 expressions of willingness.

10 DR. SHAPIRO: Is there language for Alta's suggestion?

11 PROF. CHARO: No, no.

12 DR. LO: A couple points about inconsistencies between the  
13 recommendation and the text that follows. It wasn't clear to me in the language of the  
14 recommendation, potential subjects had made it in this type of research as opposed to  
15 this specific protocol. The example given on page 139 suggests a specific protocol to  
16 which they'd expressed a willingness to participate and I think that's way too narrow. I  
17 think that we should allow families, we should allow for previous statements to  
18 participate in a certain class or type of research, not to a specific protocol. And then  
19 secondly, I just want to flag a problem that I think is on page 138, from paragraph 12 to  
20 17.

21 DR. SHAPIRO: Unfortunately, I think one of the things where either the  
22 word processing or something else has run wild is on most of 38 and top of 39. It just  
23 needs to be reassigned or rewritten. We just have to ignore it for the moment. It will  
24 either come out or it will go somewhere more appropriate. Larry?

25 DR. MIKE: Since a) and b) is an alternative to c) and d), I don't  
26 understand why we have such loose language about consent when you're expressing a  
27 willingness to participate. Whereas if you asked me, you're not going to enroll me in a  
28 research project simply on the basis that I expressed a willingness to consent. You have  
29 to get my consent. So if you can enroll someone without capacity under a) and b), the  
30 way it's written right now, isn't it too loose? You're just taking somebody's word?  
31 Shouldn't that just be straight consent, consent previously expressed and documented?

32 DR. SHAPIRO: I'd like to respond to that and secondly, I'd just like to  
33 see if there are other comments. Because I think this is an important issue. First of all, on  
34 the issue Bernie raised—or at least one of the issues he raised. On the question of  
35 whether it's a particular protocol or type. My view is that it ought to be parallel to what's  
36 on this c) and d) or c) right now which deals with a type of or nature of research. It's  
37 appropriate language, it doesn't tie it to a specific protocol. That's my own view. As I

1 recall, that's what it says under c) or I would like it to say, put it that way. I don't know  
2 whether it says that right now. Let me tell you what I've rewritten here just so as not to  
3 take the language. Let me go to c) and d) first and I'll come back up to a). What I did is I  
4 took c) and I wrote "the subject's legally authorized representative is given permission  
5 for the subject to be enrolled in the study." That's c). And both c) and d) would have to  
6 be satisfied. And d) I wrote—and this is a little informal, but I'll tell you what I've  
7 written—"the subject has not expressed ..." gosh, I'd better work on this. But the  
8 substance of it is that I want to tie it, my view, to a category of researcher, type of  
9 research, and that's my own view. Because i think it is too narrow. And I'll get back to  
10 Larry's point in just a second. Diane?

11 DR. SCOTT-JONES: I just wanted to say that on page 140, the language  
12 is, as you're saying now, Harold, where it does refer to a type of study and it says "agree  
13 to participate." Whereas the one we are on now, on page 137, just says "expressed  
14 willingness." So the language is very different on page 140 and it should be probably be  
15 more consistent.

16 DR. SHAPIRO: I agree with that. And I think—Jim, and then I want to  
17 get back to Larry.

18 DR. CHILDRESS: I would just like to connect this with Larry's, or build  
19 on it, at any rate. It seems to me the way we have this worded on 137 now, that the a)  
20 and b) extending along as providing the basis for enrolling someone in research, that that  
21 is too vague. And that really what we want there, it seems to me, is the LAR being the  
22 person who interprets the person's previous wishes or willingness to participate if we  
23 take that very broadly in understanding. Because we do have to ask the question of a)  
24 and b), who is going to be providing this information? Simply the investigator or the  
25 physician, etc.? I don't think this could really stand alone. So I don't see a) and b) as  
26 totally separate from the other if we're going to word a) and b) as loosely as we do here.  
27 Now if we move into a much more specific direction, then we do get closer to something  
28 like advanced planning that is much more direct and perhaps even includes something  
29 like informed consent. So I think we need to work on these components together and if  
30 we stay with these loose ones for a) and b), then I think we really do need to make it  
31 "and the LAR's permission." I don't think what we have in a) and b) is sufficient, would  
32 be sufficient by itself to enroll.

33 DR. MIKE: But if you follow that line, then it makes it much more  
34 restrictive. That the LAR can only approve if there has been a previously expressed ... If  
35 these are combined, then why bother with including that? If the LAR can give permission  
36 with or without some previous indication by the potential enrollee in the program, why  
37 list that in this if you're going to combine them? I'm only responding to Jim's suggestion.  
38 I still have problem with it or the way it's written.

1 DR. LO: Let me carry on with the discussion that Larry and Jim were  
2 having. It seems to me the reason for having an a) and b) or c) and d) is that there may  
3 be some people who don't have someone they feel comfortable appointing as a legally  
4 authorized representative, but may have a strong willingness to participate in certain  
5 types of research and want to express that willingness to participate in advance. It seems  
6 to me that in a clinical situation, you want to have one mechanism by which patients can  
7 give prior consent, if that's the right word, without having a third party involved. And the  
8 other track is for people who may not have just thought about the issue or made specific  
9 statements, but have a legally authorized representative who they trust or is willing to  
10 make a determination, based not on what the individuals had said about willingness to  
11 participate, but just on the basis of asking them to.

12 DR. SHAPIRO: I think that one of the key issues we have to resolve here  
13 before we're going to straighten this out, and has been pointed to by a number of you, is  
14 the issue of willingness. That is, whether that really is informative enough. First of all,  
15 will people understand what we mean? Do we understand what we mean? The  
16 alternative, which I guess that language was selected with the idea of not having required  
17 previous consent, and the question I think we have to face directly is whether we feel in  
18 the case of greater than minimal risk research, which offers some potential direct benefit,  
19 that a person who is currently incapable really can be enrolled—let's take the top  
20 one—only if they've had previously given their consent or not. If we put consent in there,  
21 that's what that would mean. And we need to address that issue. Steve?

22 MR. HOLTZMAN: It may be that we really want to roll these all  
23 together. Because if you look at b), isn't it the case that if you move down to c) and d),  
24 you'd still want b) to apply?

25 DR. SHAPIRO: Right. That's what d) was in my case, although I got the  
26 wording here wrong. It's really a version of b).

27 MR. HOLTZMAN: No, because d) has to do with the previously who  
28 didn't say they were against it. B) has to do with the notification of the assessment. And I  
29 think to Larry's point, if a) is something short of written documentation of consent of this  
30 type of research, you're turning to someone. And if that someone is saying well, they  
31 were in favor of it or even if they weren't in favor of it, I still think it's a good idea. It  
32 kind of rolls together, at least pragmatically. So maybe there's a way of doing this where  
33 either there's written evidence of documented previous consent. In the absence of that,  
34 then you have the LAR who says it's okay. The subject has been notified of the  
35 assessment—I can try writing it if you want, combine them all.

36 DR. SHAPIRO: I appreciate the offer, but let me just see where we are in  
37 the substance of the issue, particularly in regards to willingness, or do we want  
38 something stronger than that. Bette?

1 MS. KRAMER: That's the problem I'm having, is that I don't know what  
2 we mean by an expressed willingness to participate. Is it going to require a formal  
3 document? Will it be sufficient for the LAR, for the family member to come forward and  
4 say "I had a specific conversation with this person." Or, failing that, would it be sufficient  
5 for that LAR or family person to say "I knew this person intimately. These were the  
6 kinds of values that this person had. This is how this person would have responded could  
7 he or she respond to the question now."

8 DR. SHAPIRO: How do you feel about it?

9 MS. KRAMER: How do I feel about it? I think that I personally am  
10 comfortable with the clinical model. I think that when a person who has known the  
11 individual intimately comes forward and says "it's my strong feeling on the basis of what  
12 I knew of this person and the kinds of values he or she expressed that he or she would  
13 want to be enrolled." I'm comfortable with that.

14 MS. BACKLAR: There are lots of little problems here and one of them  
15 we really haven't put out on the table, which may make something of a difference to what  
16 I'm thinking about. And that is who this LAR is. Is it somebody, as Bernie says, that the  
17 persons have chosen themselves? Or is it somebody who now is appointed to make these  
18 decisions? And I don't think that we've made that clear and that would make a very big  
19 difference in terms of Alta's suggestion of using the clinical model. But there's another  
20 problem here which we seem to have forgotten about. The clinical model is okay because  
21 the person is a patient and the provider cares about the well-being of that patient in front  
22 of them. This is very different, even if there is benefit, because now no longer is that  
23 person going to be looked at directly in terms of their own well-being. What is wanted  
24 by that person in a research protocol is generalizable knowledge. And if you switch  
25 around with that person's care because they're not doing so well, you're going to ruin  
26 your research protocol. So I think we have to be very careful at every stage to remember  
27 what it is we are talking about. My question still goes back. I want to know about the  
28 LAR.

29 PROF. CAPRON: It seems to me that several of these comments are  
30 tending in the same direction, which is that the difference is not between a legally  
31 authorized representative and a patient's advance document, but it's among types of  
32 representatives and the basis on which they are deciding. That the representative who  
33 knows the patient and is deciding based upon the patient's own prior expression of  
34 precise wishes or more generalized wishes is in a different category than a legally  
35 authorized representative who doesn't know the patient. And that either of those people  
36 is in a different category when they are making this so-called best interest judgment. That  
37 is to say that the benefits here, the prospect of benefits, are sufficient to justify even  
38 without knowing that the person would have chosen this based upon solid evidence that  
39 they would have chosen this. And that that really is the difference. A further comment is

1 I don't think we need to have b) or d) here at all. We have Recommendation 7.  
2 Recommendation 7 already says you have to notify and if they dissent from participating  
3 in research, you have to respect that dissent. I think that kind of extra language here is  
4 going to keep us from addressing what is really the issue here, which is partially driven  
5 by what Trish says, with which I agree. That the pure use of the clinical model at least as  
6 to be addressed as to why it would be suitable in a research setting and why we don't  
7 need to insist upon something more for this setting. But if we're going to have a)s and  
8 b)s and c)s and make differences, I would make the contrast between what a person does  
9 when they're choosing, as a person who knows well, as Bette says, versus the person  
10 who simply says "well, it seems to me, not knowing this person at all, I'm now appointed  
11 as their conservator. It's in their best interest to be in this."

12 PROF. CHARO: I take Larry's point. I think he actually stumbled on  
13 what would might have been—

14 DR. MIKE: I never stumble.

15 PROF. CHARO: Strode forcefully upon what I think was a  
16 confusion—captured eloquently—a confusion between our goals in this section and our  
17 goals in the section with non-beneficial research. I think that the discussion about the  
18 role of the LAR actually is quite revealing because the issue of willingness to participate  
19 and other kinds of less formal expressions are all rolled into the legitimacy of the LAR's  
20 decision to enroll an incompetent subject into research. Because that is supposed to be  
21 premised upon a best estimation of what that person would have done for himself or  
22 herself if still competent. So I think it's entirely possible to redraft 8 and 9, as Steve was  
23 suggesting, together to simply say that these protocols can be approved if the potential  
24 subject consents at the time of enrollment. Or the potential subject has consented, as you  
25 would say, genuinely consented in the past while capable of informed consent. Or c), is  
26 being enrolled by a LAR who is acting appropriately. And appropriately is acting as one  
27 assumes that this person would have acted for himself or herself. I don't recall if we've  
28 got a separate section that speaks directly to the kind of decisionmaking tree for LARs  
29 and how it is that they are supposed to start with what the person would have wanted to  
30 do and only move secondly to a kind of best interest analysis. But if that's not there, we  
31 could either create that as a separate section or we could try to roll in here. I think it may  
32 be best to—

33 PROF. CAPRON: But you would allow it, the best interest judgment. I  
34 don't know this person, but on balance it looks like it would in be the best interest.

35 PROF. CHARO: No, no. First, my understanding, I think it's very  
36 important that we keep in mind that the LARs are not going to be strangers. They are  
37 not going to be court-appointed strangers and they are not going to be institutions.  
38 Second, that the LAR's role as a surrogate decisionmaker is to do what the person would

1 have done for himself or herself. That means first, you start with what they've expressed  
2 in the past, which can encompass things that are idiosyncratic. And if they've not  
3 expressed things in the past, then I think that friends and family are entitled to make  
4 assumptions that people would act generally in their own best interest because most  
5 people do. So you start with what people have actually said or indicated, and if it's really  
6 vague on that, you can, I think, empirically safely assume that they would act in their  
7 own best interest. And that's why you've got a hierarchy. You start with what they've  
8 said, and then you move to kind of best interests only secondarily. And this thoroughly  
9 allows them for all of these situations, consent, prior consent, or LAR permission, to  
10 incorporate the notion of seeking assent where it's appropriate, respecting dissent at all  
11 times. And as an integrated model, I think it gets away from this problem. Finally, I think  
12 the question about the language about willingness to participate in that vague language I  
13 think is going to become very important in the next section of non-beneficial research.  
14 That's where, I think, it's going to become a subject of real discussion where we assume  
15 that there's been no prior consent and the question is on what degree of knowledge of  
16 the person is necessary to enroll them in research that has no prospect of direct medical  
17 benefit. And maybe that's the place to take up that discussion, what degree of formality is  
18 needed.

19 DR. MIIKE: Let me just state it real simply. The only difference that  
20 should be, in my mind, in this area where there's either benefit or not in this greater than  
21 minimal research is the ability of somebody else to consent for the subject. So therefore,  
22 in this area and in the following area, the proof of a subject consenting directly should be  
23 exactly the same. And we should use the language that I believe is on 10. Because in 10,  
24 it lays out very explicitly what's proof of a subject and then it says nothing about LARs  
25 being able to approve. So the only difference between this one and the next one should  
26 be the discussion around the LAR. Because if we get into the kind of discussion we're  
27 getting into now, we're talking about a different type of LAR for this area from the other  
28 side.

29 DR. SHAPIRO: I think this has been a very helpful discussion and  
30 clarified a number of issues. Just to reinforce the strategy I want to use today, I'd like to  
31 ask at the next break that Steve, Larry and Alta take a shot at this and another version of  
32 Recommendation 9. Steve, I'll put you in charge so you have to mobilize this at our next  
33 break. Okay. Let's now go on and at least have an initial discussion and see how far that  
34 takes us with respect to Recommendations 10 and 11 which are, in some sense, parallel  
35 to 8 and 9, only dealing with the situation of greater than minimal risk that does not offer  
36 the prospect of direct medical benefit. Trish?

37 MS. BACKLAR: Just before you move on. I just wanted to make sure  
38 that we've agreed that this LAR is somebody who has been chosen by the subject. Is that  
39 correct? We're not moving to the next recommendation, the recommendation we were  
40 just talking about.

1 PROF. CHARO: I did not choose my mother as my legally authorized  
2 representative but, under many State laws, she would be because I'm not married.

3 MS. BACKLAR: So you have children of an Alzheimer's patient who are  
4 anxious to get this person off their backs.

5 MS. FLYNN: I have to object to that, I really do. I think that there is a  
6 tone that runs through this that assumes that family members in this situation are not  
7 going to be acting in the best interest of their relatives. And I think that everything we  
8 know tells us that that's not the case. And we should assume that, as we do in all clinical  
9 situations, that people who are involved in long-term caregiving with a chronically ill  
10 person care about that person and not assume that they don't. There certainly are cases,  
11 of course, but we don't want to build a whole structure around exceptions and assume  
12 that this is supportive of good decisionmaking.

13 DR. DUMAS: But you also don't want to avoid making provisions for  
14 certain controls in cases where that might not be, in situations where that might not be  
15 the case. So I think the point that we're making is that we believe that this category of  
16 people need to have added protections and the emphasis is on the added protection. I  
17 don't think we should ignore the possibility that even a family member might not be as  
18 objective as would be warranted in that situation. That's not to assume that all family  
19 members would not be, but I don't think we ought to go to the opposite extreme, either.

20 MS. FLYNN: Well, this will just be a place where we'll disagree. Here  
21 we're talking again about research that is expecting to be of benefit to the patient.

22 DR. DUMAS: Yes, but consider that—I don't conceive of this argument  
23 as being about whether or not the patient should participate in research that is potentially  
24 beneficial. Our argument has to do with when the person can't make their own decision,  
25 what kind of safeguards need to be provided in order that people who do make the  
26 decision do so in the best interest of the person?

27 MS. FLYNN: And again, I'm stating that I believe in that circumstance,  
28 we can and we should trust families. That patients can dissent, that there are other  
29 protections we've built in earlier and that families who are legally authorized  
30 representatives in almost all cases should and can be trusted to make good decisions.  
31 And that there's very limited risk involved in research here that is seen as having direct  
32 medical benefit.

33 PROF. CAPRON: I have a question, since there seems to be such  
34 disagreement about what we're talking about. Not just the wisdom of it, but what we're  
35 talking about. In the discussion around page 81, about the legally authorized rep, I don't  
36 see anything there that says the legally authorized representative as a family member

1 necessarily was involved in caretaking for the patient. It may simply be in the view that  
2 Alta expressed that the relative is usually turned to. Although it isn't true in most States  
3 unless they have a statute that says this that any adult is automatically the legally  
4 authorized rep. It's the custom to turn to a spouse or a parent, but there's no common  
5 law in that at all except for minors, that I know of. But this discussion, the legally  
6 authorized rep, is all around the person who, as Trish was assuming, is appointed in  
7 some fashion. And the questions that we raise about that are how much documentation is  
8 necessary, how much clarity is necessary. That the person you're choosing could make  
9 this or that decision about you. The kinds of things which now exist in durable power of  
10 attorney for health care statutes, where they have to very clear. You're giving this person  
11 permission basically to decide about life and death for you. And all of that suggests that  
12 the legally authorized representative means authorized by the subject. But the reaction to  
13 which I don't think we have any recommendation that clarifies this, was no, that it would  
14 include people who are placed in that role by custom or because they've gone to court, I  
15 guess, and had their informal status formally recognized. Those are very different  
16 relationships, it seems to me. And I agree with Laurie that it is very likely that most  
17 family members who have been in a caring relationship know their subject better than  
18 others and are motivated to see the subject get whatever benefit research could offer.  
19 But we don't here require that there be any, as it were, assessment of that or even any  
20 requirement that the person have been an active caretaker. As opposed to Mrs. Jones,  
21 you were listed on the form as Steven Jones' mother, you are his mother—that's right.  
22 You haven't seen him for awhile, but we want to enroll him in research which we think  
23 will be beneficial to him. Will you give us permission? Yes, I will. That would also fit  
24 within this. And that relative may be a loving person or may be neglectful. May be  
25 knowledgeable about the person's wishes, or may not be. And we don't differentiate that.

26 MS. BACKLAR: I agree with Laurie that families are usually the best  
27 people to go to. But for instance, I just wanted to say that I have a very large family and  
28 there are people in that family who I would trust to care for me when I no longer have  
29 the capacity to do so, and there are people in my family who I would say "I love you  
30 dearly, but I don't think you're going to be the person to do this." So this blanket, saying  
31 people are all right is what concerns me. That's really what I'm after.

32 MS. FLYNN: But I don't see how we can parse this out effectively unless  
33 we start giving psychological tests to family members. Unless we start credentialing  
34 people in terms of the most recent time that they spent more than an hour with the  
35 individual. I mean, either families generally have the welfare of their kin in mind, or don't.  
36 Certainly the closeness of the relationship often speaks to that level of dedication, but  
37 not always. And certainly caregiving often speaks to the closeness of connection to the  
38 person's wishes, but not always. We either believe, as we do in clinical settings, that  
39 families ultimately care enough about their relatives to sort out their personal wishes  
40 from what they believe to be the good of the person who is incapacitated. We permit this  
41 in a clinical setting. We recognize the extraordinary reliance of the individuals we are



1 most concerned about on family members for many aspects of their ability to live in the  
2 community. And yet we're not so sure we can rely on them to enroll subjects who are  
3 incapacitated in research that may benefit them. I'm having trouble understanding why.

4 DR. SHAPIRO: There are a number of people who want to speak, and  
5 then we're going to move on until we get a new look at this recommendation. Larry,  
6 Alta, Jim, Eric and Arturo.

7 DR. MIKE: This discussion seems to me to be around a real simple  
8 issue, whether the LAR must be appointed by the subject or not. If we limit it to just an  
9 LAR that the subject thought capable appointed, I think we're really going to be cutting  
10 back on the research. So are we just going to make a decision of whether we  
11 particularize an LAR? You can have the clearer notion that what we're talking about is...  
12 we have LAR. I'm not simply limited to one designated by the person himself or herself. I  
13 guess one question, though, that arises for me, and that I have a way to deal with the  
14 kinds of exceptional cases as they've been called, there are ways to disqualify LARs.  
15 LARs may not be competent, for instance, to make decisions. LARs may not be, may  
16 have given evidence that they're acting against the best interests of the person and so  
17 forth. Now, some of those, some State statutes, and I'll have to let the lawyers in the  
18 group tell me if it's right or not, presumably have some of those things that we're doing  
19 certainly about competence. But part of what we're talking about here would be there  
20 may be situations where we'd want investigators, and this may be a matter of advice  
21 rather than of something we could recommend for regulation, we'd be attending to those  
22 sorts of issues. So that even though we start with a presumption, given that by the legal  
23 structure as well, in favor of the legally authorized representative as structured by that  
24 legal context. There may be situations in which basically we seek to disqualify the LAR.

25 DR. CASSELL: I just want to briefly lend my voice to Arturo and  
26 Laurie. It's generally and for the most part, the question isn't are families nice or not nice.  
27 It's the alternative. Generally and for the most part, is a stranger or a family member  
28 more likely to be beneficent in regard to the person? And I think that the family members  
29 are. And that's just the way it is. The fact that some people screw you is just also the way  
30 it is, but—.

31 DR. BRITO: I agree with Alta about the similarities between the clinical  
32 arena and research. But I do feel uncomfortable with the parallels, or extending them too  
33 far. In a clinical arena, when a physician or healthcare provider has, in the best interests  
34 of that patient, they are usually resorting to new trials of medication when they're really a  
35 last resort. But in research, okay, in research that there is hope, that there is direct  
36 medical benefit. You could be putting the patient at risk, and making their—especially  
37 when we're talking about greater than minimal risk—you'd be putting that patient at risk  
38 that is subject to making their life worse after the research. I just don't feel real  
39 comfortable with these parallels. Because I think that there's a big distinction between

1 clinical work and research. And maybe Alta you could explain what—I wouldn't feel  
2 comfortable saying—and this goes along with the LARs. If an LAR is told by a physician  
3 that there is a chance, there is a chance that by placing their, who they're representing, at  
4 greater than minimal risk, with some sort of prospect, they, even if they have the best  
5 interests of that patient, which would be in most situations, I agree with that, they could  
6 still be, they may not be as objective as they would in a clinical arena. I'm not explaining  
7 this very well, but I just don't feel real comfortable with that parallel and using that here.  
8 I don't know.

9 DR. MURRAY: I want to address two points. In the discussion about  
10 whether to give a kind of specialist's moral status to legally authorized representatives  
11 chosen by the subject, that we should admit the possibility that prospective subjects  
12 wouldn't always choose wisely. Or even the personally chosen LARs would always act  
13 out of, you know, for the best interests of the subject. Granted, it may be there's maybe  
14 somewhat, you may be a little bit more confident if they're hand-picked, but we shouldn't  
15 be entirely confident. So it's not a matter of either/or, it's really a matter of degree.  
16 Second point is, as I think about the purpose of the document we'll be writing, it has  
17 primarily on researchers and on the people who are regulating the actions of researchers,  
18 rather than on the behavior of subjects or their representatives. That is, our document, if  
19 the recommendations are implemented, ought to prevent researchers from performing  
20 research on people with impaired decisional capacity. That might be harmful to those  
21 people, or otherwise not in their interest. And we would want to prevent researchers  
22 from doing this either out of ignorance or insensitivity, out of indifference, or certainly  
23 out of malice. Which we don't expect researchers to show. Insofar as the document we  
24 write will bear on the families, the legally authorized representatives, we can certainly  
25 help prevent them from agreeing to research based on ignorance by insuring that they are  
26 informed properly. It's not clear to me that anything we could do could check an LAR  
27 out of indifference or malice. I mean, the most we can try to do is alert researchers and  
28 others involved to be sensitive to that, and if they see that happening, obviously, to try to  
29 be responsive to it.

30 DR. SHAPIRO: Now let's listen to Bernie, and then we're going to stop  
31 discussion on this now. You'll have more chances later.

32 PROF. CAPRON: It is certainly true that a representative who is making  
33 a poor decision, either because they're incapable or because they don't seem to be taking  
34 the interest of the subject into account, could be disqualified. But for the reasons that  
35 Arturo and Trish have focussed on, we should recognize that the incentives in the case of  
36 a person providing clinical care, to institutes, such a disqualification are very different  
37 than in the research setting. And I don't think it is, as Tom just said, any assumption that  
38 researchers would be operating out of any malice or evil thought. They are operating and  
39 motivated by the desire to prove that some treatment is going to work. But that isn't the  
40 same as being focussed only on the welfare of the patient. And therefore, I think that the

1 assurance that you suggest that we can be pretty comfortable because people who aren't  
2 deciding the right way will be knocked out of the picture. It's just the other way around  
3 here. The person who objects to the subject being used might be found to be the person  
4 who, well, why are we listening to this person? Let's get somebody else in here who will  
5 understand the benefits of what we're talking about more.

6 DR. LO: Let me take a crack at trying to find some common ground here.  
7 I think we're all recognizing that we can set a general presumption or assumption, but we  
8 have to take into account the fact that there are going to be some families, legally or  
9 authorized representatives, who don't act the way we would hope and want to act. I  
10 agree with Alta and Eric and Laurie that we should start from the generality that legally  
11 authorized representatives will follow the patients' wishes and act in their best interests.  
12 Then how do we take into account the fact that some won't? And Arturo and Pat very  
13 rightly point out that in the clinical setting, there are some automatic safeguards built in.  
14 Let's look at those safeguards. What we can't capture in these regulations is the face-to-  
15 face discussions. In a clinical arena, it's the doctor talking with the family or the  
16 representative, trying to explain, making sure they understand. Sort of probing, you  
17 know, what their motives are, how close they've been, things like that. We can't regulate  
18 that. And I agree that in the research setting, the assumptions about the stance of the  
19 researcher have to be somewhat different than the assumptions we make about the  
20 treating physician in a clinical setting. But I think that there are other tools that we have  
21 for providing safeguards. And we've talked about them elsewhere in the report. Consent  
22 monitors to make sure that when this legally authorized representative consents,  
23 someone else is there to listen in on the discussion. Make sure that the way they make  
24 decisions fits with this model, following the patient's previous statements or best interest.  
25 I think trying to involve an independent physician who is not part of the research team to  
26 talk with the legally authorized representative to try to make sure they've informed and  
27 not under a therapeutic misconception is something else we've talked about. But I'm not  
28 sure I'd put it in the regulation, but there are certainly are other things that we've already  
29 laid out that IRBs may choose to do for certain protocols, certain types of studies that  
30 would, it seems to me, go a long way toward affording the protections that Alex and Pat  
31 and Arturo are rather concerned about, where the analogy with the clinical situation  
32 backs down. I think again you have to look at the alternative. Is the alternative to make  
33 it so restrictive that basically a lot of people are going to be closed off from participating  
34 in this category of research?

35 DR. SHAPIRO: I'm sorry, we're going to have to stop discussion of this  
36 now. But let me just remind you, for those of you who will be writing, Steve, the head of  
37 the group and Alta and Larry and Eric, to rework this to try to incorporate some of the  
38 very interesting and useful comments that have come out here. And I'd like to do that so  
39 we could turn back to that early, right after lunch at 1:00 we could come back to this.  
40 And Trish, I know you have other things to say. You're welcome to join this group,  
41 incidentally, and maybe that's an effective way. But also, you could bring it up at 1:00

1 when we get back and discuss this. So I'm sorry—I just want to move on. Let me just  
2 remind the Commission that in roughly 10 minutes from now, even a little less than that,  
3 we do have public comments and that's really an important part of our day today. So  
4 we'll be turning to that very shortly. Let's see if we can't have at least an initial discussion  
5 of what are, in some sense or another, a parallel set of recommendations that are in here,  
6 but this time dealing with greater than minimal risk research that does not offer the  
7 possibility of direct medical benefits to the subject. And I'm not going to attempt to  
8 describe Recommendation 10 for you—it's parallel to 8. Recommendation 11 is different  
9 but parallel, in some sense, to Recommendation 9. Maybe we could have at least a few  
10 initial comments no this as to how the Commissioners feel about 10 and 11. We could  
11 put 10 to bed if you like. Let's talk about 10, first of all. Diane?

12 DR. SCOTT-JONES: I just have a question about the way it is worded,  
13 especially compared to Recommendation 8. It states that an IRB may approve, if the  
14 person with the capacity to give informed consent to participation, has done so. It reads  
15 that the consent would have been given before going to—

16 DR. SHAPIRO: I agree with that. That's a problem with 8, too. Any  
17 other comments on 8? Let's see if there are some initial comments on 11, which requires  
18 3 conditions to be fulfilled. Any comments, questions—Larry?

19 DR. MIKE: Only that I think this should also be the test of 10 with the  
20 "with benefit" and the "greater than minimal risk." That this is what I think should be  
21 used in place of that willingness to participate.

22 DR. SHAPIRO: You'll have a chance with Steve to work all that out after  
23 the break. Any other comments on 11? Bernie?

24 DR. LO: Well, I think maybe we could first ask if anyone thinks that if  
25 conditions a), b) and c) are fulfilled, the person may not be enrolled in the study. So my  
26 concern isn't that I would object to someone who fills a), b) and c) being enrolled. The  
27 question I have is that the only way you may enroll a subject in this type of study? But  
28 maybe just to start we should see if there are even things that even if this were met, you  
29 wouldn't permit this type of research for this. So I think we have to get to 12 a) and b).  
30 In my mind, I don't have a problem with 11 as long as I know what the alternatives are.

31 DR. SHAPIRO: That's a useful initial comment and we do have to allow  
32 some discussion when we get to 12. I should mention in general that there are, as many  
33 have noted already, interrelationships some times between these proposals. So when we  
34 go through a proposal, that doesn't mean we can't come back to it if, on the basis of what  
35 we do later, either it changes it or it doesn't look quite right. And so we have a package  
36 at the end which has to be looked at in its own right. So that's something that is really  
37 quite important so thank you for mentioning it. Diane?

1 DR. SCOTT-JONES: I have a question about what we mean by this type  
2 of study. And also, in other places in the recommendations when we say this category of  
3 study, does it refer only to what's laid out in the heading? And the category would be  
4 studies that present greater than minimal risk and do not offer the prospect of direct  
5 benefit. That's what's meant by type of study. It isn't meant to be type of study in a  
6 substantive research sense. It's that heading there.

7 MR. HOLTZMAN: Category refers to the italics, type refers to the type  
8 of research.

9 DR. SHAPIRO: I can tell you how I interpret it, type. I think it's really  
10 important we use this vocabulary appropriately, as Steve has indicated. I had thought not  
11 of the whole category of research, greater than minimal risk, no potential benefit. That's  
12 not what I thought type referred to. I thought it referred to a class of research not  
13 completely easy to define which was similar, let's say imaging studies of various kinds  
14 and that's what type meant. So you wouldn't have to insist on having it down to a single  
15 research protocol, but a type that had roughly the same kind of procedures involved,  
16 roughly the same levels of risk and benefit without being able to define it exactly. But in  
17 my view, it didn't refer to everything under this category, which is any research project  
18 that was greater than minimal risk with no potential benefit. That's just how I interpret it,  
19 but this is open for discussion. Bette?

20 MS. KRAMER: Then would your understanding preclude a person who  
21 has just expressed a willingness to participate in a prospectively beneficial research  
22 period, or would they had to have specified the type?

23 DR. SHAPIRO: This is not prospectively beneficial.

24 MS. KRAMER: Excuse me, I didn't use the language properly. I didn't  
25 mean beneficial to the individual. In an otherwise approved research. In other words,  
26 how specific would a person's expression of willingness have had to be to qualify within  
27 your understanding?

28 DR. SHAPIRO: In my understanding, I can't draw the boundaries exactly,  
29 that would be up for the IRBs to look at more carefully. But it's a kind of protocol that is  
30 roughly similar kinds of procedures, similar kinds of risks and so on that would be  
31 available so you'd have some basis on which the consent was granted. I don't want this to  
32 be, or at least my interpretation was, it was not a blank check for everything in this  
33 category.

34 MS. KRAMER: Would that presuppose a fairly sophisticated  
35 understanding of what research might look like down the road?

1 DR. SHAPIRO: Well, if it changes very dramatically, then a) doesn't  
2 hold, the way I interpret it. Because you have a dramatically different type of research  
3 then you wouldn't be covered by this. This is just the way that I interpret it and that's  
4 why this table is open for discussion. Larry then Alta, then we're going to have to break.  
5 We'll come back to this, obviously.

6 DR. MIKE: Actually now I'm having problems with this. What I'm  
7 comparing this is to, say, I'm being asked to enroll in a research project that has nothing  
8 to do with mental illness or behavioral research. And they say "well, we're going to be  
9 doing a series of studies and it's going to involve a bone scan." And I say "yes, that  
10 sounds great." That would never stand up as my consent when we actually get into the  
11 study. So it seems that I would rather have these cleanly defined. Because everything in  
12 b) and c), it follows that we're not talking about this type of study. How can we talk  
13 about this type of study if we also we've said that there's no material change in the major  
14 research protocol, etc.? So it seems to me that the simplest way to do it, as long as we  
15 have the discussion around 12 about exceptions to the general rule. It seems to me that  
16 to be clean, both Recommendation 11 and 9, there needs to be a consent to that  
17 particular study contemplated. Because in prior discussions over the past year or so, we  
18 have been talking about—it had to be really close to the time of the study that that  
19 person became incapacitated. We couldn't talk about 1 or 2 years before that and they  
20 would generally say "oh, I wouldn't mind participating in MRI studies" or whatever. I  
21 thought we had come to the conclusion at that time that that was too far removed. So  
22 I'm looking at this and saying that this type of study is not really satisfactory to me. It's  
23 really got to be consent to a particular protocol, the research we're talking about.

24 PROF. CHARO: Just to give you an idea of how troublesome this is  
25 going to be after lunch, I'd like to argue for the far end of the spectrum, away from  
26 where Larry is. I'd like to argue for the blank check approach. I'd like to argue for those  
27 few people who actually bother to express their wishes prospectively, being able to say  
28 "I want to be used." And if they want to make limitations based on levels of pain or  
29 variations of interventions, they are free to. But they also should be allowed to say "I  
30 want to be used." And that there needs to be in here, actually, a stronger statement about  
31 the role of the representative in giving permission consistent with that prior expression of  
32 wishes. Because I find the possibility of specific consent to specific protocols to be so  
33 rarely usable that it eviscerates this provision. And I think that if there's any hope for  
34 integrating this discussion into the larger discussion about exactly how protective we're  
35 going to be of people who've made no expression of wish, then I think we need to be as  
36 expansive as possible about people who would like to express their willingness in general  
37 to altruistically serve as a research subject. So they are very much related to the  
38 afternoon discussion.

39 DR. SHAPIRO: Trish was bursting before and is still bursting ...

1 MS. BACKLAR: Actually, it's because I agree and it affects what I  
2 wanted to say before. I think if the people make a choice, then it's their choice. And if it's  
3 clearly made, they may make it as they wish as long as they're not going to harm  
4 somebody else. But the same concept applies in terms of choosing somebody to speak  
5 for you. And I just wanted to say that this "Being Researched" by Greg Sachs on people  
6 who, in fact, may already have dementia but are capable of saying "this is a person who I  
7 trust and they can make the kinds of decisions that I'm now no longer capable of  
8 making." That's all. The choice is what counts.

9 **PUBLIC COMMENTS**

10 DR. SHAPIRO: Thank you very much. We are now going to move into  
11 our public comment section and we have a series of people who have signed up which  
12 will use up all the time we have allocated. Before public comments, I want to remind all  
13 those who give public comments that there is a limit of 5 minutes and out of courtesy of  
14 those who come after you, please stick to your 5 minutes. I will let you know when your  
15 time is almost up. There have been various requests of people who seem to want to  
16 appear in various orders. I'm just going to take this in the order in which they registered.  
17 First come, first serve is the only kind of fair way to deal with this, so I'll just ask for a  
18 couple of comments from those in the order in which their request arrived with our staff  
19 at our office. The first person to speak will be Harold Pinkus, Deputy Medical Director  
20 of the American Psychiatric Association. Dr. Pinkus?

21 DR. PINKUS: The American Psychiatric Association, on behalf of more  
22 than 40,000 psychiatric physicians nationally, appreciates the opportunity to comment on  
23 the NBAC draft. The guiding principle in our comments is that the interest of  
24 participants in research projects comes first. We appreciate the careful and thoughtful  
25 deliberation with which the Commission considered these issues as evidenced throughout  
26 the report. We agree with the Commission that more attention must be paid with regard  
27 to research conducted with persons of potentially impaired capacity and we support  
28 many of the recommendations of the Commission. However, we would like to focus our  
29 concerns and our comments today on three areas which we believe should be modified.  
30 As recommendations are currently drafted, important research will be precluded without  
31 providing significant additional protections, an outcome we don't think is intended by the  
32 Commission. With some additional modifications, these recommendations could prove  
33 beneficial. Our previous conversations with staff have been very productive and we hope  
34 to continue them so we can continue with the shared goals that we think we have with  
35 the Commission: to provide protections and assure added increments to our knowledge  
36 about mental disorders. Many of the concerns we raise today are shared not only by  
37 other researchers, but also shared by consumer groups as well. To mention one example,  
38 30 national mental health groups, including several of the leading consumer and family  
39 groups, wrote the Commission last Thursday. These groups, including the APA, stated  
40 our support for many of the Commission's recommendations, but urged that the report

1 not focus on individuals with mental illness, but instead focus on individuals with  
2 impaired decisionmaking. We also particularly call your attention to the October 8th  
3 comments of the National Depressive and Manic Depressive Association, as well as  
4 NAMI's testimony supporting a more graduated approach to research risk, instead of a  
5 two-tiered approach. Our specific concerns are as follows: 1) requiring capacity  
6 assessments for every research participant be performed by an independent expert is  
7 highly impractical and will not provide meaningful protections for participants with  
8 mental illness. Individuals with mild depression or anxiety or sexual dysfunction, primary  
9 insomnia, adjustment disorders—all conditions like that are diagnosable mental  
10 disorders—are not likely to have a higher incidence of impaired decisionmaking than the  
11 general population of potential research participants. Particularly in these cases, the  
12 highly burdensome requirement of an independent capacity assessment simply does not  
13 make sense and could compromise valuable research. Also, many individuals, even with  
14 severe mental disorders such as stabilized bipolar disorder who are functioning quite well  
15 will find this requirement intrusive and offensive. Similarly, it appears from your  
16 recommendations that independent competency assessment would also be presumed  
17 even in minimal risk research, such as questionnaire or observational studies. This would  
18 seriously divert resources in situations in which subjects are essentially at no risk from  
19 participation. We also recommend that the Commission review the APA policy statement  
20 entitled "Guidelines for Assessing the Decision Making Capacity of Potential Research  
21 Subjects with Cognitive Impairments." 2) We believe NBAC support for a two-tiered  
22 level of risk in the regulatory framework i.e., minimal risk and greater the minimal risk,  
23 should be modified. Limiting the calculation of risk in research to these two categories  
24 would seriously harm the abilities of scientists to conduct research, particularly research  
25 presenting a very low level of risk that potentially may yield important breakthroughs in  
26 our ability to treat mental illness. Others have identified important areas of research that  
27 would be compromised in this area. We urge NBAC to adopt a more graduated level of  
28 risk rather than a simple two-tiered approach. Third, we also believe, and probably most  
29 importantly, that your approaching the report, focusing exclusively on individual with  
30 mental illness, unnecessarily stigmatizes these individuals and is not based on our current  
31 scientific understanding of these illnesses. We are troubled that this focus appears  
32 conceptually flawed and logically inconsistent. While the report alludes to the definition  
33 of mental illness in DSM-IV, it is unclear to readers whether the Commission intended  
34 for conditions that affect central nervous system functioning, but are not commonly  
35 considered as mental illnesses, to be included. If the Commission intended their inclusion,  
36 then the mental disorders label is not only stigmatizing, but confusing, and does little to  
37 help investigators identify those at risk given as noted above, the vast majority of  
38 individuals with mental disorders have mild, less-impairing conditions. A more accurate  
39 term would be disorders that affect decisionmaking or disorders that affect the  
40 functioning of the central nervous system. If the Commission did not intend for these  
41 disorders to be included, then their logic for failing to do so is not clear. Why should an  
42 individual with a stroke or diminished cognitive function from congestive heart failure be  
43 afforded less protection than somebody with Alzheimer's disease or schizophrenia? What



1 is the essential difference? If you are recommending special accommodations for  
2 individuals who can't climb a flight of stairs, you wouldn't have a focus on individuals  
3 with cardiovascular conditions, thus including people with hypertension and no  
4 impairment and excluding people with impairing pulmonary or neurological or other  
5 conditions. The costs of these categorizations are high. Not only is there serious  
6 stigmatization of a class of individuals on the basis of their condition, but there are  
7 important practical implications that undermine the Commission's overall goals. What the  
8 report—inadvertently diverting attention from assessing capacity to evaluating mental  
9 illness. There is also the point that future progress and understanding in treating mental  
10 disorders requires both financial and intellectual resources. The diversion of resources  
11 for unnecessary added protections in low-risk situations was discussed earlier. A more  
12 serious and subtle diversion is likely to result from the greater perceived barriers in  
13 mental illness research, diverting talented young people into other lines of research or  
14 out of research altogether. There are already significant barriers, intellectual barriers,  
15 many of which are identified by the Commission's report. While these, maybe in some  
16 cases, are stimulating intellectual changes, consider the plight of a talented young  
17 medical student interested in research, looking ahead to a career path requiring extensive  
18 research training and foregoing a more lucrative clinical practice. Additional stigma and  
19 barriers unique to mental disorders research as a class are likely to diminish the relative  
20 attractiveness of the field, reducing the already limited flow of talent to a very leaky  
21 pipeline of research career development in mental illness. We urge the Commission to  
22 modify its title, report and recommendations to focus on conditions that may affect  
23 decisionmaking capacity and to not apply blanket requirements to individuals with mental  
24 disorders. We share with the Commission your goals or providing additional needed  
25 projections to individuals with impaired decisionmaking, and look forward to working  
26 further with the Commission.

27 DR. SHAPIRO: Thank you very much. We very much appreciate your  
28 coming today. Larry?

29 DR. MIIKE: Let me ask you, does the existence of the American  
30 Psychiatric Association stigmatize people with psychiatric illnesses?

31 DR. PINKUS: We don't believe so. But I think there's a fundamental  
32 difference here.

33 DR. MIIKE: You've answered my question, thank you.

34 PROF. CHARO: Oh, Larry. May I ask that he continue with his response,  
35 for me?

36 DR. PINKUS: There's a fundamental difference here. Here you're  
37 essentially significantly, in my view, illogically singling out a particular class of

1 individuals on the basis of a particular impairment that is shared by other classes of  
2 individuals. And that's, I think, an important problem.

3 DR. SHAPIRO: Thank you very much. Next to speak is Dr. Leslie  
4 Alcorn, Consumer Council President, present member of Board of National Alliance for  
5 the Mentally Ill. Mr. Alcorn, thank you for coming here today.

6 MR. ALCORN: Thank you. Did you say Doctor? I'm afraid not. I want  
7 to thank the committee, Mr. Chairman, for this opportunity. First, a couple of  
8 clarifications. I am not coming to you as someone who is anti-research or anti-  
9 medication or anti-psychiatry. In fact, I support many of those things and take  
10 medication myself that has lifesaving qualities for me. So I need to clarify that. Also, I'm  
11 not here to have some narrow political posturing or organizational infighting. But I can't  
12 argue that the dynamic does exist, but please accept my remarks in the context of the  
13 bigger picture. I don't believe in this august body—and I mean that truly—I don't believe  
14 I can inform or reveal any great truths. After reviewing earlier testimony, it's clear that  
15 the issues have been spelled out. I wouldn't consider it. ... or the well of philosophical  
16 and ethical traditions that have produced the ancient verities. Nor am I persuaded that  
17 you're in possession of all those facts as it relates to the field of bioethics. Perhaps it's  
18 lost in the minutiae of syntax and deliberations, but I want to remind everyone exactly  
19 why we have commissions, why we have standards, why we have oversight. Why we  
20 have bodies designed to do that, entities. It's because there's evil in the world and that's a  
21 fact. There's rapacity, there's single-minded self-interest, duplicity, co-option, human  
22 frailty and, all too often, massacre of the innocents that comes from that. That's why  
23 you're here. You're here to protect the defenseless. You're a line of defense against all  
24 that I've previously invoked. That's why I come before you today. I'm a relatively recent  
25 student of bioethics, but I will tell you the research that I've done, no pun intended, I  
26 found it absolutely horrifying. So totally antithetical to my career as an advocate, where  
27 I've worked to get people on medicine, to get the right medicines, the right amounts. To  
28 give them the quality and to return their humanity. And then I discover a particular  
29 branch of experiments called psychosis-inducing experiments with challenge studies,  
30 drug washouts. How about a little ketamine with your coffee in the morning? Carbon  
31 dioxide with your bagel? You can cloak this in all the lab coats and academia and sterile  
32 scientific language you want, but this is evil. These kinds of experiments are evil, and  
33 they are experiments. There was evil 50 years ago, it will be evil tomorrow and it will be  
34 evil 1,000 years from now. And if I know that, then you folks must know it too. And  
35 please don't forget why you're here. A doctor who remains unnamed claimed 50 percent  
36 of folks with schizophrenia lack insight. But these psychosis-inducing experiments, there  
37 seems to be no problem with that batting average—it's very, very high. So the  
38 interpretation of what's informed consent and what is not is very alarming. I want to  
39 conclude by saying I think it's fairly obvious to me that we are here trying to facilitate  
40 research. And in the process of enthroneing that, we are attempting to provide some  
41 minimal standards of decency for the human beings that are involved in it. And I would

1 submit that that's exactly the opposite of what it should be. We should be attempting to  
2 define and defend the sanctity of the individual and then put the research around that.  
3 But we seem to have got things backwards here. I don't believe it's possible to maximize  
4 the research capability on consenting disabled human beings and protect the sanctity and  
5 inviolability of the individual. You either must err on the side of one or on the side of the  
6 other. And this has every appearance on erring on the side of science. There's nothing  
7 sacrosanct about research. There's everything sacrosanct about the individual, the human  
8 life. Let's spell it out—there's billions and billions of dollars tied up in this business.  
9 Pharmaceutical money, university grants, research and that is driving, pushing, riding this  
10 entire process. That's what is not being discussed here, that's what is kind of  
11 unmentioned or between the lines.

12 DR. SHAPIRO: I don't mean to interrupt, but are you nearly through?  
13 Could you wrap up your remarks?

14 MR. ALCORN: Yes, sir. Today you debate the sanctity of human life.  
15 Humanity has always faced grave consequences when we have had the arrogance and  
16 suicidal audacity to do so. And I would end with a quote from Shakespeare, paraphrase:  
17 "Hath not a consumer eyes, hath not a consumer hands, organs, dimensions, sense,  
18 affections, passions, fed with the same food you are, hurt with the same weapons,  
19 subject to the same diseases, healed by the same means, warmed and cooled by the same  
20 summer and winter as you? If you prick us, do we not bleed? If you tickle us, do we not  
21 laugh? If we poison us, do we not die?" Thank you ladies and gentlemen.

22 DR. SHAPIRO: Thank you very much and thank you for coming such a  
23 distance to speak to us. I very much appreciate it. The next speaker is Miss Kathy  
24 Mannion, Fort Washington, New York.

25 MS. MANNION: Good morning, everybody. My name is Kathy Mannion  
26 and I'm here today to represent two of my children who are incapable of representing  
27 themselves. My son Brian, age 9 and Daniel, age 8, have autism. Their younger brother  
28 Patrick, age 7, has been diagnosed with Asburger's Syndrome. Their older brother  
29 Michael, age 11, is a perfectly healthy and normally developing child. Living with autism  
30 is typically a life-long struggle for both the child and the family. Children are unable to  
31 communicate and have great difficulty understanding language. They are unable to learn  
32 even the simplest of things on their own. They engage in ritualistic, often bizarre,  
33 sometimes violent and even self-injurious behavior and they require constant supervision  
34 and teaching. For families like mine, life is often something to survive rather than to be  
35 enjoyed. Autism is not episodic; there are no periods of normalcy. It is indeed constant.  
36 My purpose for being here today is to convey to you the tremendous need for ongoing  
37 and scientifically sound research in the field of autism. Although the vast majority of  
38 persons with autism would be considered incapable of ever understanding or providing  
39 informed consent, good, ethical, humane, scientific research has yielded very promising

1 advances in the treatment of childhood autism. But this is only because their parents and  
2 guardians have been free to allow them to participate in such research. I learned many  
3 years ago while working at Memorial Sloan-Kettering Cancer Center, that whenever  
4 there exists a condition for which there is no known physiological cause or cure,  
5 desperation and vulnerability pave the way and create a haven for pseudoscience. This, in  
6 fact, is true in autism. It is a field that is littered and, in fact, dominated by  
7 pseudoscience. The presence of ongoing and scientifically sound investigation is sorely  
8 lacking and the absence of the dissemination of accurate, scientifically validated  
9 information has not only allowed pseudoscience to flourish, but to prevail. When we first  
10 entered the world of autism, my husband and I were not at all prepared for the complex  
11 maze that we would have to navigate in order to get an accurate diagnosis and timely  
12 and effective intervention for Brian, and later Daniel. They were evaluated by a vast  
13 array of professionals and were labeled speech impaired and language delayed. The  
14 unanimous recommendation was for both of them to be enrolled in early intervention  
15 programs. Although they began intervention at less than 2 years of age, they made little,  
16 if any, progress in the first 3 years of their remediation. During this time, my questions  
17 and our decisions were governed by what I knew to be true in medical science. When I  
18 asked about a definitive diagnosis, we were told that we could not get one. When I asked  
19 what the research indicated on types of interventions and their effectiveness, we were  
20 told that there was none available. The more I pushed for answers, the more frequently I  
21 was referred to various support groups. It was my experience that in the field of mental  
22 health, the focus was more on helping parents to cope rather than helping them to find  
23 the information they need to make informed decisions about the best possible care and  
24 intervention for their children. It took three years to finally access what scientific  
25 investigation had already proven to be the most effective intervention for children with  
26 autism. Once Brian and Daniel began to receive it, they not only began to learn, they  
27 began to thrive. Had it not been for science, I don't know where they would be today.  
28 Because of pseudoscience, I will never know where they could have been. Brian and  
29 Daniel and countless of other people with autism will probably never have the cognitive  
30 ability to provide informed consent to any type of scientific investigation. If parents and  
31 legal guardians do not have the right to provide consent for them, people with autism  
32 will be almost categorically deprived of the benefits that scientific research provides.  
33 However, scientific investigation is the only hope that people with autism have. Without  
34 it, they and their families are doomed to a life of agony and significant disability. As a  
35 parent, I applaud your efforts to protect the rights of those who are incapable of  
36 protecting themselves. I would respectfully ask, though, that the committee give careful  
37 consideration to autism and developmental disabilities like it where there are no episodes  
38 of normalcy, and informed consent could not ever be granted unless by parent or  
39 guardian. Without this proviso, scientific study in this field can be virtually eliminated. I  
40 ask that in your efforts to protect our children, you do not unintentionally deprive them  
41 of the one and only hope that they and their families have for a better life and a brighter  
42 future. Thank you.

1 DR. SHAPIRO: Thank you very much and once again, I very much  
2 appreciate you being here today. The next speaker is Jacqueline Shannon, President of  
3 the Board of National Alliance for the Mentally Ill.

4 MS. SHANNON: I'm a little shorter here. Dr. Shapiro and NBAC  
5 Commissioners, I'm Jackie Shannon of San Angelo, Texas and I'm president of the board  
6 of directors of NAMI, formerly the National Alliance for the Mentally Ill. As you know,  
7 NAMI is the largest grassroots organization of people with severe mental illnesses and  
8 their families in the United States. We presently have 185,000 members and 1,300  
9 affiliates all across the country. You may be interested to know that all NAMI board  
10 members are either consumers or family members, and we represent the many diverse  
11 viewpoints of our membership. I myself am the mother of a son with schizophrenia, so I  
12 know firsthand what a devastating illness schizophrenia is and what it can do to  
13 consumers and family members. I also know that research is very important and it is so  
14 for consumers and their families. I am here today to express NAMI's support for many of  
15 the recommendations contained in your draft report. I must express, however, NAMI's  
16 concern that at least one of your recommendations may pose significant and unnecessary  
17 barriers to vitally important basic research. And I believe this was already mentioned by  
18 the APA. As you know, NAMI has been a long-time supporter of research and research  
19 funding by the Federal Government. And we've also supported two privately funded  
20 research organizations, the National Alliance for Research on Schizophrenia and  
21 Affective Disorders, NARSAD, and also the Stanley Foundation program of the NAMI  
22 Research Institute. Our members know and we well understand that research represents  
23 the best hope we have for treating and eventually curing severe mental illnesses. At the  
24 same time, though, we understand the vulnerabilities of people who participate as human  
25 subjects in this research on severe mental illnesses. Thousands of NAMI family members  
26 have participated in research and continue to do that today. Not only to gain possible  
27 access to cutting edge treatments, but also to assist in learning information that can  
28 benefit other people with severe mental illnesses in the future. We understand that many  
29 people with severe mental illnesses are perfectly capable of making their own informed  
30 choices to participate in research. But we also know that the symptoms of schizophrenia  
31 and bipolar disorder and other brain disorders may, from time to time, impair the ability  
32 to make informed decisions or to balance the potential benefits and risks of specific  
33 research protocols. Over three years ago, in fact in February of 1995, after extensive  
34 debate and consultation with scientists, bioethicists and others, NAMI became one of the  
35 first national organizations to adopt a policy which sets forth recommended standards for  
36 protecting individuals with severe mental illnesses who participate as human subjects in  
37 research. In fact, Dr. Adil Shamoo, a member of the NAMI board at that time, played a  
38 key role in the development of this policy, along with Laurie Flynn, Jay Rock Johnson, a  
39 current NAMI board member and the former chair of our consumer council, and Ron  
40 Hamburg, NAMI's legal director. And if you are interested, a copy of this policy is  
41 available on the table outside this room for those who wish to examine it in greater  
42 detail. We're pleased that your draft report contains a number of recommendations

1 contained in our policy. For example, the recommendation that all IRBs which review  
2 and provide oversight over research involving people with mental disorders as human  
3 subjects should include members with firsthand knowledge about these disorders,  
4 including people with severe mental illnesses and their family members. We view the  
5 ongoing participation of consumers and families in review and approval of research as  
6 the cornerstone of a partnership that affords protection for human subjects. And we're  
7 also pleased that your draft report recommends that independent assessments of capacity  
8 monitoring of research subjects occur throughout the research process. This is very  
9 important. And this was also included in NAMI's 1995 policy. As is your  
10 recommendation that participants in research be free to withdraw consent at any time in  
11 the process, with or without a stated reason. And finally, we're pleased that the NBAC  
12 report emphasizes the importance of affording individuals who benefit from experimental  
13 medications the opportunity to continued access to these medications after research  
14 protocols terminate. We've had a number of such studies in Texas, and that's been a very  
15 important issue, that consumers are able to continue with these medications. We're very  
16 proud that NAMI's work has provided such an important impetus for your own work.  
17 However, I must emphasize NAMI's concern that the NBAC report potentially  
18 jeopardizes certain types of essential research by recommending only two classes of risk:  
19 minimal risk and greater than minimal risk. For example, basic research involving  
20 relatively low-risk procedures such as PET scans, MRIs, EEGs and other imaging  
21 studies may be precluded under your approach because these procedures are typically  
22 classified as greater than minimal risk. We have continually urged that you apply an  
23 intermediate category, which would be minor increment above minimal risk to research  
24 of this nature. However, since you have chosen not to do this, we recommend an  
25 alternative that you might delineate a list of your research procedures involving scanning  
26 and imaging techniques in your report that should be classified as minimal risk.  
27 Otherwise, despite its numerous positive recommendations, it's going to be very difficult  
28 for NAMI to support your final report. We cannot afford to erect unnecessary barriers to  
29 low-risk but vitally important research. And today, you're putting the final touches on a  
30 report that will impact significantly on future research policies and practices. I urge you  
31 to make sure that what you put forward is properly balanced. That no individual suffers  
32 unnecessarily while participating in research. But also, so that a healthy climate is  
33 maintained to allow critically important research, our best hope to proceed. And in  
34 closing, I want to reiterate how honored I am to have the opportunity to speak to you as  
35 the president of the nation's largest consumer and family organization representing  
36 individuals with severe mental illnesses. And let me also emphasize of how proud NAMI  
37 is of the selection and ongoing participation of Laurie Flynn as an NBAC Commissioner,  
38 and we're also very pleased that Trish Backlar, a member of the NAMI family, has  
39 contributed her considerable wisdom throughout the NBAC process. And finally, let me  
40 say how confident I am that progress, both in research and in research protections, will  
41 assure that future generations will not have to endure the suffering that my son has. And  
42 thank you very much.

1 DR. SHAPIRO: Thank you, and thank you very much for being here  
2 today.

3 PROF. CAPRON: Would you entertain one question? You indicated your  
4 suggestion that a list of research procedures involving scanning and imaging techniques  
5 be classified as minimal risk. In our discussions, we have tended to think that whether the  
6 risk was minimal or not might depend upon other aspects of the study going on and the  
7 category of patient or even individual characteristics. If our procedures were to allow  
8 that to be taken into account, would it meet your concerns? Or do you really believe that  
9 procedures can be categorized as minimal or not, regardless—

10 MS. SHANNON: There are certainly a number of procedures that could  
11 be categorized as minimal risk. Of course the best approach would be to have a three-  
12 tiered process.

13 DR. BRITO: Just one quick question. I'm just curious, out of your own  
14 experience, when we were discussing defining the two categories or three categories of  
15 minimal risk, one of the issues that comes up is psychosocial risks. And in terms of  
16 procedures, what is your experience in terms of psychosocial problems experienced by  
17 people with severe mental illness when exposed to certain procedures? Or is that a  
18 concern?

19 MS. SHANNON: I'm not quite sure I follow you. Psychological risks?

20 DR. BRITO: Right.

21 MS. SHANNON: I don't know if I have an answer to that.

22 DR. SHAPIRO: Thank you. This next speaker is Dr. James McNulty,  
23 Treasurer of the National Alliance of the Mentally Ill.

24 MR. McNULTY: I'll do my best, but I do have to correct one  
25 misapprehension that I'm a doctor. I'm also not a doctor, but there are a lot of them in  
26 the room, so I feel like we're in good hands. I have some prepared remarks, so if I do  
27 have to leave before I'm done with them, please feel free to grab them. I have to respond  
28 to a couple of issues that have come up in the testimony of other people, some of which  
29 I found very profoundly moving and affecting. I would also like to state at the outset,  
30 however, that I dislike the implication that I've picked up today that people like myself  
31 who are consumers—I suffer from bipolar disorder—are unable to act in our own best  
32 interests or out of a sense of altruism. And whether you realize it or not, that is a  
33 message that I have been picking up in many of the discussions that are taking place here  
34 today. I did like Ms. Charo's suggestion of a broader interpretation to consent, and that  
35 in fact is something that I've done myself in my advanced directive for health care or I've

1 directed that I would be willing to participate in various forms of clinical research. My  
2 record in the past indicates that I've participated in double-blind placebo drug studies, as  
3 well as lithium trials to determine the difference in effectiveness between lithium and  
4 depecote on the treatment of bipolar disorder. Now I'll proceed with my prepared  
5 remarks. I come before you today representing several viewpoints that I hope you can  
6 keep in mind as you move toward adoption of your report. I am president of the Manic  
7 Depressive and Depressive Association, known as the MDDA, for short, of Rhode  
8 Island. I serve on the board of directors of NAMI and I also serve as an IRB member at  
9 Butler Hospital, a psychiatric hospital in Providence, Rhode Island, where research is  
10 conducted in association with the Brown University School of Medicine and with other  
11 institutions. Behind all this, and the main reason for my involvement in these  
12 organizations, is the fact that I do live with a diagnosis of bipolar disorder, a disease that  
13 I have learned to manage thanks in part to the expansion of medical knowledge over the  
14 last quarter century. One of the reasons I came to NAMI in the first place is NAMI's long  
15 history of advocacy for research into the causes and treatment of serious mental illness.  
16 Having at one time been homeless and without much hope myself, I know the hope that  
17 research presents to those of who experience these illnesses and to our family members.  
18 In the end, it is biomedical research that will bring us to the point when we can truly say  
19 we have conquered mental illness. This is, of course, true of many illnesses, but it is a  
20 particularly important point to bear in mind as society becomes more comfortable with  
21 the understanding that mental illnesses are indeed physical diseases and disorders. My  
22 work the MDDA and with NAMI brings me in daily contact with many other people  
23 with psychiatric diagnoses. Among other things, I facilitate peer support groups attended  
24 by others with bipolar disorders and other psychiatric disorders and have done so for  
25 over 10 years. I'm very familiar with the hopes and concerns of those who attend. You  
26 will have to believe me then when I tell you that the foremost complaint coming from  
27 people with bipolar disorder that I know is that there are simply not enough effective  
28 treatments for this illness. There are only two medications that have been approved by  
29 the FDA for the specific treatment of bipolar disorder. As a NAMI board member, I am  
30 proud of the work that NAMI has done to encourage research in this area. Having noted  
31 the scarcity of activity in bipolar research, the NAMI Research Institute is developing an  
32 extensive bipolar treatment network. At the same time, I am pleased to note that NIMH  
33 is acting on NAMI's recommendations to move forward with the funding of more bipolar  
34 disorder research. Both efforts hold promise for those like me and I hope set an example  
35 for other research funding sources to follow. I've also discussed the need for more  
36 research with numerous other consumers from across the country who are involved with  
37 the NAMI movement and some who are not. They believe sincerely that far more  
38 research must be conducted if future generations are to be spared the pain suffered by so  
39 many of us in our struggles with these illnesses. And for many of us who live with mental  
40 illnesses, involvement in research programs is perhaps the most significant way in which  
41 we find we can make a positive contribution to the society in which we live. We feel  
42 privileged that we can act as partners in research in a way that neither doctors nor  
43 academic researchers nor our friends or family can. This opportunity to be part of



1 something larger than ourselves is desired by many of us who have so often been beaten  
2 down by our illnesses. Many of us, in fact, do this knowing full well that the findings of  
3 the research in which we participate are not likely to help us directly. And of course we  
4 all participate knowing that there are risks associated with being part of an experiment.  
5 The point where the research meets the risk is the elusive quest of this Commission. And  
6 speaking as someone with an illness and as someone who has participated in clinical  
7 trials, I wish to make it clear that I do find some risk both acceptable and necessary.  
8 How am I doing on time?

9 DR. SHAPIRO: If you could draw your remarks to a close.

10 MR. McNULTY: I will wrap up then by having laid preface to all of this,  
11 I would make the following points. I think there do need to be improvements in the  
12 informed consent process, more involvement of families and I think a better appreciation  
13 of the ability of consumers to be involved in it. Making clear distinctions between  
14 research and clinical care. Affording ongoing access to treatment after a project is done,  
15 which is very critical in today's environment of managed care. And I think really  
16 involving consumers and family members on IRBs, I would urge this Commission to  
17 really make that more of a directive than something that's optional. Thank you very  
18 much.

19 DR. SHAPIRO: Thank you very much for being here. Questions?

20 PROF. CHARO: You mentioned your participation in clinical trials. I  
21 wonder if I might ask you a couple of questions about that experience? The trials that  
22 you described are trials that definitely have some risks associated with them—they were  
23 drug trials. They also offered the prospect of some personal benefit in case you got a  
24 drug that worked better for you. Were you ever invited to participate in research that  
25 had no prospect of benefit to you, but had risks that were in the order of what you  
26 experienced?

27 MR. McNULTY: Well, the second study I was on was not a direct risk.  
28 One of the problems with bipolar disorder in particular is that we note that medications  
29 often stop working for people somewhere along the line. And that's why I got involved  
30 in the second study, which is the lithium versus depecote study. But there was some  
31 proximate benefit to myself; I have to be honest. I have asked myself the question  
32 "would I be willing to act out of a sense of pure altruism?" And my answer is affirmative  
33 to that and I offer as an example my Uncle John who died of melanoma, very painfully I  
34 might add, and participated in a number of clinical trials until he felt he could no longer  
35 live with it, at which point he said "that's it—let me go." And when I thought back to  
36 that example, that's more or less what I used in my own decisionmaking framework.

37 PROF. CHARO: But you've never actually volunteered for such a non-

1 beneficial research protocol yet.

2 MR. McNULTY: As a member of the IRB at Butler Hospital, I have yet  
3 to see one come across that could be characterized as not having direct benefit to the  
4 subjects.

5 DR. SHAPIRO: Thank you very much. The last speaker today is Miss  
6 Catherine Klapp, FragX Research Foundation in Massachusetts.

7 MS. KLAPP: Thank you very much. I am President of FragX Research  
8 Foundation, which is a advocacy organization which supports research on Fragile X  
9 Syndrome. My two children have Fragile X Syndrome and I started this organization 5  
10 years ago with my husband and we have about 1,000 families now. Basically what we do  
11 is support research aimed at an eventual treatment. So must of us feel very strongly that  
12 we would like to keep this research moving forward. You may know that in Fragile X  
13 Syndrome, like autism, most of the individuals are not likely to be able to give informed  
14 consent. My son Andy will never be able to give informed consent. So therefore, it is  
15 going to basically be my job to make decisions for him throughout his life and that has  
16 been the case so far. I'd like to speak from the point of view of a parent looking at your  
17 recommendations and feeling that you may unintentionally throttle the very research that  
18 offers us hope. We, if you will, test medications all the time. Andy has quite a bad  
19 seizure disorder as part of the Fragile X. This has meant several helicopter trips into  
20 Boston and six or seven medications, one after another, all of which so far have failed.  
21 The newest one that heps on was not available several years ago when he had his first  
22 seizure and so we, it was our own son, are already benefiting from the kind of trials that  
23 may not happen if this language goes through. An important point I would like to make  
24 about this is that children with Fragile X and other children with disorders like Fragile X,  
25 do not respond the way most children do to standard medications. Ritalin, for example,  
26 acts quite differently in Fragile X. And this is all lore because I happen to be president of  
27 this organization and my husband, as a psychiatrist, has kind of become a specialist in  
28 this disorder. We have doctors and parents calling us from all over the country desperate  
29 for information on what of the available drugs they can use for Fragile X syndrome and  
30 there is nobody of medical literature to help them. There are no double-blind studies but  
31 there is lore and the lore seems to work but it's also quite a frightening feeling to be  
32 experimenting on your own child. It's just that that's where we kind of are right now  
33 and what needs to happen to change that is some good proper studies on children that  
34 have the problem that you are trying to address. And in this case, it means Fragile X. It  
35 means participating in studies which may have some risk. There is no chance of getting  
36 informed consent. I would like to suggest that the people best qualified to give that  
37 consent are the people closest to the individuals involved. In this case, the parent or the  
38 guardian. If you think about it, in our society, it is the parent or the guardian who has  
39 this responsibility for all sorts of other decisions for sending this child through life as  
40 positively as possible. And so I'm concerned when I see recommendations that some

1 impartial observer needs to be brought in from outside and make this judgment when I  
2 really think that it is the parent or guardian that is most qualified and most responsible  
3 for making these decisions. So I see it as something of a rights issue. Andy's right to  
4 participate. My right to make the best decisions I can for him. Thank you very much.

5 DR. SHAPIRO: Thank you. I appreciate your remarks. If you would  
6 wait a moment there's at least one question someone would like to ask.

7 PROF. CHARO: I want to make sure I understand where exactly your  
8 discomfort lies and what you feel we've lost. What's been proposed so far would  
9 absolutely allow a guardian to volunteer somebody into research that has a lot of risk so  
10 long as it also had some possibility of personal benefit.

11 MS. KLAPP: That's what concerns me and in an effort to keep remarks  
12 short, I didn't elaborate on that, that I think it is very hard to prove in any given study  
13 that that study could have direct benefit to the individual involved. Now in the case of a  
14 seizure medication, it could have direct benefit. However, as president of Fraxo, we are  
15 also supporting team therapy and demethylation studies and so on and so forth, and  
16 those are studies that are directed at what is close to a cure. And participants in those  
17 studies may have no immediate benefit to gain from participating even though there may  
18 be some risk. And just as the previous speaker said, that he would make the choice, an  
19 altruistic choice, to participate when he knew he had nothing to gain. In this case, I need  
20 to make that choice for Andy and I feel that I'm the one who's best positioned to do  
21 that. And the truth is that I already do make those choices when I, you know, get us into  
22 the newspaper and tell them that my daughter has Fragile X and therefore label her as a  
23 mutant when she has no symptoms. I have made a choice that may hurt her because it  
24 really needs to be done otherwise we're just not going to get anywhere, and I, so I'm  
25 really very concerned that we are not going to be able to progress past the stop gap,  
26 seizure, Ritalin, sort of measures to something that really could help.

27 DR. SHAPIRO: Thank you very much. I very much appreciate you being  
28 here. We're going to recess the meeting now. Let me suggest that we try to reassemble  
29 at quarter after one. Steve, you have a group that you have to somehow mobilize and  
30 maybe you can do that around one.

31 DR. SHAPIRO: Pick up some additional copies in a few moments to  
32 pass out to interested people, but Steve, due to time, why don't we get started.

33 MR. HOLTZMAN: Sure. We were asked to look at the question how  
34 would we deal with recommendations effectively 8 leading up to 12 and the conceptual  
35 organization of them. If you look, 8 started out with the research that presents greater  
36 than minimal risk and offers the prospect of direct benefit and that was the general  
37 category of recommendations 8, and 9 and then we went on to 10 and 11 where there

1 wasn't a prospect. So the flow chart in front of you really suggests how we reorder a  
2 bit our thinking, and that we start with the global category of greater than minimal risk,  
3 put aside for the moment whether there is prospective benefit. The first question that  
4 seems to be at stake is, is the subject capable of consent, yes or no. If yes, then after they  
5 have given their consent you can do the research. If they're not capable of consent, the  
6 next question is, did they give prospective consent to the protocol and if you look in  
7 Recommendation 11, there seems to be some ambiguity: 11a represents the prospective  
8 consent as being to a type of study, whereas 11b talks about changes in the specific  
9 protocol and it seemed to us that if we're going to keep intact the concept of consent,  
10 let's keep it full-blooded, that it should be prospective consent to the protocol that's in  
11 question. I'll come back to why we think that's okay. If there has been prospective  
12 consent to the protocol, again where we are dealing with someone who is not capable of  
13 concurring consent, then you can go ahead but there has to be a role for the LAR to  
14 monitor what's going on. On the other hand, if there wasn't prospective consent to the  
15 protocol, now you conceptually move down to the question is there the prospect of  
16 direct medical benefit. Eric, could you push that up now? So, if there is a prospect of  
17 benefit, and here again we are in the absence of consent or prospective consent, then you  
18 can go ahead with the research if the LAR approves and here, Alta suggests that we flesh  
19 out our expectations of the LAR. That the way they should be thinking is if there were  
20 previous general expressions of desires or wishes, not to a specific protocol but to a type  
21 of research, that would be taken account of. Failing that, move to another standard of  
22 the best estimate of the subject's wishes based on the knowledge of the subject and then  
23 last, in general, best interests, presumably because there's a prospective benefit. And,  
24 once again, the LAR should monitor. Now, it's only then we move on the other side of  
25 this. Well, what if there isn't prospective benefit and then we land at Recommendation  
26 12.

27 PROF. CAPRON: The question for clarification under LAR approves,  
28 and this was I thought the point that Larry, same kind of point that Larry had insightfully  
29 discovered and I think that you may have all—

30 DR. MIKE: I stumbled on it.

31 PROF. CAPRON: No, no. And they may have all stumbled off of it. Are  
32 we saying that, in what sense other than the language, is there any priority to these three  
33 that are listed here because, if, you could always go with best interest.

34 DR. MIKE: I think we meant that it is sort of sequential. If there was a  
35 previous expressed wish then we would pay attention to that. If not, then the best  
36 estimate and then finally the best interest.

37 PROF. CAPRON: But I guess my point would be we usually conceive of  
38 this as a situation in which we are merely giving guidance, for example, around end-of-  
39 life decisions, if the wishes are known. In some jurisdictions, the decisionmaker can't

1 act unless the wishes are known by clear and convincing evidence and so forth. But  
2 where there's a best interest alternative, the reason for going with the other is that that  
3 ethically is what accords with the notion of a substituted decisionmaking process. But  
4 other than the relatives all aiming for that, there's really no enforcement process that  
5 pushes anybody toward that. I mean, the courts don't see most of the cases and the  
6 IRBs aren't going to see most of the cases. I'm not objecting to the notion that we  
7 would expound in favor of this but this seems to me to be something that would not be  
8 in the recommendation as such.

9 DR. MIKE: It's not.

10 PROF. CAPRON: I thought this was all going to be you do this and then  
11 you do this and you do that and it seemed—

12 DR. MIKE: We also talked about we've got to keep our  
13 recommendations fairly short and simple.

14 PROF. CAPRON: So this is merely descriptive of what would be the  
15 ideal; that when you do know what the person wanted, you ought to decide that way. If  
16 you know, as Bette was saying, a lot about someone, they'd never express wishes on  
17 this, you do that and when you don't know, you go with best interests. Okay, so that's  
18 fine. But we're not saying that anybody is in any position to actually regulate this other  
19 than on good faith.

20 DR. DUMAS: I have a concern about prospective consent to a current  
21 protocol and it would make me feel better if we called it prospective consent to research  
22 related to the protocol because, it's conceivable, that the patients might be recruited for  
23 a project that was not anticipated when they gave their consent so it might not be to a  
24 particular protocol but to research that's relevant to the protocol.

25 PROF. CHARO: I'd like to speak directly to Rheta's point because  
26 it's related, I think, to the question of the language of the LAR and it's related to  
27 Larry's first point that he so elegantly captured. What's been drafted is the following  
28 kind of image of events. People give informed consent to very specific things that have  
29 been specifically described. Now they also say I want to be put into research that  
30 involves MRI but don't put me into research that involves spinal taps. The research  
31 protocol that comes down is one that has to deal with PET scans, neither MRIs nor  
32 spinal taps, we have no specific direction. What this then says is that their representative  
33 is supposed to use everything that they have to develop their best estimation of what this  
34 person would have chosen under the circumstances and to effectuate that person's  
35 genuine wishes. And in this way, you can give consent to very specific things, but all the  
36 other statements you make about research that's related to but different from the one  
37 that is being proposed, etc., is in the use of the LAR, it's in the LAR's hands to use

1 when they try to figure out if you yourself would have volunteered if presented with this  
2 option. That's the image of how this would work.

3 DR. DUMAS: It seems to me that would make me feel even stronger  
4 that the consent that's being given is to research and not to a particular protocol.

5 DR. MIKE: I thought what you were talking about was the right arm  
6 that said yes to the question. What Alta was responding to was it gives guidance to the  
7 LAR in case there was no consent. And I feel as though that one cannot say that we can  
8 go down the right arm saying yes there was consent if there's this general notion that  
9 they consented to some kinds of research rather than something more particular like a  
10 protocol. And the way Alta has defined protocol is fairly liberal. It wasn't what I'm  
11 thinking but I can accept that definition. I was thinking of a specific study but I can  
12 accept what Alta is saying.

13 MR. HOLTZMAN: I should say that I was using shorthand by protocol  
14 up there simply to distinguish it from some sort of broad of idea of "I'm in for  
15 research." And that if you look again at section 11 when we talked about approval of  
16 types of research and then we started talking about specific protocols, there seemed to  
17 be an ambiguity, at the least, between of how we seem to be thinking in  
18 Recommendation 11.

19 PROF. CAPRON: So now we're using the word protocol in two ways.  
20 Most of the time in this report we say an IRB may approve a protocol. What we mean is  
21 a research plan for this research. You're now using the term here and maybe we should  
22 use a different term. Steve. I'm addressing Steve. Was using the word protocol playing  
23 off of what you said Alta to say a protocol is a category of intervention. Is that right? To  
24 say MRIs but not spinal taps? Let me first ask Steve what he means and then we can  
25 decide. That's what I was asking. And then we can decide whether we want this word  
26 or another word but I think it is a critical issue.

27 DR. SHAPIRO: We better stop on it and decide, and I think Tom is  
28 eager to make a comment before you speak, Steve.

29 MR. HOLTZMAN: Let me phrase the three options in front of us with  
30 respect to what we are calling prospective consent. It's either narrowing to a specific  
31 protocol where one can envision all of the risks and benefits, and the objective of the  
32 research. It could be something somewhat broader than that to what we call variously a  
33 type of research, all right? Or it could be even broader than that. What I think we were  
34 thinking of or what I was thinking of here is that there has to be a certain narrowness for  
35 it really to be consent and since the backdrop we're going to be deferring or have this  
36 potential to go down to the LAR approval that it was better, in my mind, not to weaken  
37 the concept of consent. Keep it narrower; how narrow I'm not—

1 DR. SHAPIRO: Let me just make sure I understand. You in your own  
2 mind are uncertain between the first two possibilities, or against the third possibility but  
3 you're uncertain. Let me just ask other members of that group who got together what  
4 their sense of it is before we see what other Commissions have to say. Alta.

5 PROF. CHARO: My sense of it was that in the prospective consent we  
6 were talking about consent as narrow and specific as consent that is given concurrently,  
7 no distinction. Take a particular protocol as to the way the word is used in an IRB  
8 review, but of course, very rarely are people going to be in a position to give consent to  
9 a particular protocol. So what is going to happen is that all the rest of the stuff that they  
10 say about how I'm willing to—this might be where I might have confused you—if they  
11 say yes, I'd be willing to have MRIs but not willing to have spinal taps or I'd be  
12 willing to have bladder muscle biopsies but I wouldn't be willing to have open heart  
13 surgery. All of that stuff is what gets fed into the third-party decisionmaker. It's not  
14 about consent. All that is about quite controlling guidance to the third-party  
15 decisionmaker. So there should be no loss.

16 DR. SHAPIRO: You put in a new word. Controlling guidance.

17 PROF. CHARO: Well, didn't we say that they are supposed to do what  
18 the person would have chosen to do so if the person said I do not want certain things  
19 that they are not going to be enrolled in certain things?

20 DR. SHAPIRO: Let me—before we get down to just leeway, or lack of  
21 leeway, the LAR has, I want to stick on this informed consent issue at the top of this tree  
22 or towards the top of the tree. I understand what you just said about the things, informed  
23 consent as we normally think of it. What would your view be about what we should do  
24 with this if someone had said, executed a document, that said I want to participate and  
25 lists a fairly lengthy list of things that they're willing to participate in which  
26 characterizes it in various ways, I don't know how to characterize things. What  
27 standing would that have in this area? Would it lead to the yes or to the no? I just want  
28 to know what's on your mind. I'm not suggesting.

29 PROF. CHARO: It would not be consent but it would certainly still  
30 permit their representative to say this person would want to be involved.

31 DR. MIKE: So it would go down in the no category.

32 DR. SHAPIRO: Unless it's protocol-specific and the way we talked  
33 about it throughout this report, I'm just trying to clarify what you think on that or what  
34 any of you that are drafting this think, it would go down the no branch although Steve is  
35 a little uncertain about that. Right, Steve?

1                   PROF. CHARO: How could you be uncertain? I'm the one that wanted  
2 the blank check and you talked me out of it.

3                   DR. MIKE: In the past discussions that we've had about what it means  
4 to have prospective consent, I seem to recall we even were talking about really the  
5 potential enrollee in our experiment, had been talked to about that experiment either by  
6 the investigator or other. So it was very specific.

7                   PROF. CAPRON: This is the kind of thing that can only be done when  
8 you are in this stage of your illness. At that point you won't be able to give consent. We  
9 wouldn't want to enroll you, however, unless you'd agreed to do it, so let's talk  
10 about it now. So it's a limited type of research. It wouldn't even probably be someone  
11 who is in the early stages of Alzheimer's saying something because the research that  
12 would be done in four or five years is not likely to be describable exactly today. Is that  
13 all correct? So, it's a very limited, very, very limited view.

14                  DR. SHAPIRO: Well, I think we need to discuss that issue because I  
15 think it is a very important issue and that is and let me just characterize this as the view  
16 of this group although you may have some differences between, among you as the case  
17 may be—that under this, if you just look at this framework, which I think is a decent,  
18 useful framework which will lay out the recommendations that perspective consent in  
19 this tree, I mean it is reading to a specific protocol and it's that, the answer's yes,  
20 okay. If it's no, then it's in the LAR's hand. What to do subject to what everyone  
21 might want to say about the LAR. So that means, in this case, that greater than minimal  
22 risk where consent is not available at the current time and no prospective consent in the  
23 same sense of the word has been given, then it's the LAR who makes the decisions.  
24 That's what this says. Let's have some comment. I'm sorry. Did I misstate it?

25                  DR. MURRAY: Where this scheme makes the biggest difference and I  
26 may just—tell me if I've gotten the facts all boggled up but an MRI, where the person  
27 has said in general I think that once I am totally unable to consent, I have no objection to  
28 your study. I would be happy to have studies done like this but an MRI is regarded as  
29 greater than minimal risk. And, in this case, there's no potential benefit to the subject  
30 but they have consented to this specific protocol. That takes you down to the lower right  
31 in the box that says you can't do it.

32                  DR. MIKE: Yes it does. Greater than minimal risk. They gave a kind of  
33 general consent, in fact, enthusiastic general consent but they didn't say yes to the  
34 protocol and there's no benefit to the person, that's a no.

35                  DR. SHAPIRO: Maybe you got a special dispensation.

36                  MS. KRAMER: No, I just, I just am confused. I want to make sure I



1 understand this. So you're saying it's okay if it's protocol-specific, the LAR now.  
2 The LAR has discretion over protocol-specific, types specific but not research in general.  
3 In other words, you're denying that blank check.

4 DR. SHAPIRO: If I could just, I think the issue with the LAR or just not  
5 at all really has to do with prospective benefit. So if there's a prospective benefit, all  
6 this leads to the LAR.

7 MS. KRAMER: Right, exactly. But I'm saying then over what kinds of  
8 decisions does the LAR have jurisdiction? And, if I understood Alta correctly, or the  
9 group correctly, they said the LAR could consent to a specific protocol. Could consent  
10 to a specific type.

11 PROF. CAPRON: No, no. The LAR steps in to give permission in lieu of  
12 consent once a specific protocol is up. The other categories were all in the early stages.

13 MS. KRAMER: No, no. I realize that. But I'm saying in terms, in terms  
14 of assessing what might have been the expressed or generally expressed or generally filed  
15 to a best estimate, best interest of the subject. That they can make a decision within  
16 those interests on a specific protocol or a specific type of research but not research in  
17 general.

18 DR. SHAPIRO: Could I help out here? I think they can make a decision  
19 for any protocol that comes along that satisfies this.

20 PROF. CAPRON: It has to be some specific protocol when they make  
21 their decision. And they can draw on those statements that weren't precise enough to  
22 be consent to a protocol but which are good advice for them. We still haven't gotten to  
23 Alta slipping the word "controlling." That those advisees are controlled.

24 DR. SHAPIRO: But let's see what others have to say. Look, let's,  
25 there are lot of people that want to speak but I would really like to see if there is some,  
26 give some time to people who have some trouble with this as opposed to people who  
27 think it's a wonderful idea. Bernie.

28 DR. LO: I continue to be troubled by this type of research that does not  
29 offer a real prospect of benefit to that individual but offers the promise of really  
30 important understanding in the condition. It is not minimal risk in any plain meaning of  
31 the word and no one seems to like the idea of it just a little more than minimal risk, but  
32 we foreclosed that here except for this number 12 bypass. If a person, while still  
33 competent, says you know, I went to all those NBAC meetings, I read their reports, I  
34 understand their concerns and doggone it I really want to be able to be in a study that  
35 helps other people. I'm willing to have a spinal tap or I'm willing to have an MRI scan

1 or have a PET scan. That was allowed under Recommendation 11 in the, as I read it, on  
2 page 140 and now this scheme forecloses that. And I think that we're saying that this  
3 option 12a, 12, and I'm just really concerned that anything that takes it out of the  
4 decisionmaking capacity of an individual that's still competent to have a say and groups  
5 it into a secretarial commission or a special IRB mechanism is a very, very different kind  
6 of procedure. And, I'm just, I'm just disturbed that there's this type of research that  
7 on some intuitive level, I think, many people feel is very different than the kinds of  
8 challenge studies, drug holiday studies, that we were talking about as being very  
9 problematic and yet we're foreclosing it here even if the patient, as best as you can  
10 anticipate what a protocol is going to be a couple of years in advance, or six months in  
11 advance. We're saying, no, it's not going to work in this.

12 DR. SHAPIRO: Let me just say that on Bernie's reference to  
13 Recommendation 11, what distinguishes that recommendation from this and the context  
14 of Bernie's concerns is "A" under 11 talked about type of study as opposed to  
15 particular protocol. So it does make a big difference which way you go at it and we're  
16 going to have to decide which way we want to go at it. I'm sorry. Larry then Eric.

17 DR. MIKE: You know, our presentation is incomplete because we  
18 haven't talked about Recommendation 12. And it just depends on whether, what side  
19 you're looking at that at. Are you looking at 12 as a really big, huge hurdle and only  
20 can be done at the secretary's level or are we talking about a modified waiver process,  
21 which makes it a lot more flexible which I think some of the kinds of things we've been  
22 discussing by e-mail, the alternative 12a, some combination of 12 and 12a. But if we  
23 allow some general notion or some general statement about future research, then we're  
24 making it easier to enroll people in with a lesser consent than I would give to some other  
25 research. So it just, it just does not seem right to me that we loosen that in those areas  
26 where it's saying greater than minimal risk, no benefit, and we make it easier to enroll  
27 them with a much lower standard of consenting than I would be in the similar situation.  
28 That's why we have this dilemma, because we've tightened up 11 in terms of the  
29 meaning, the definition of actual consent. Really the proof of the pudding is that what we  
30 are talking about is a rare exception, or are we talking about a much more reasonable  
31 alternative to enrolling people into these experiments which has greater than minimal risk  
32 and no benefit?

33 DR. SHAPIRO: Let me just say something before turning to Eric.  
34 Obviously, these issues are interrelated, as Larry just indicated, and so whatever way we  
35 go at this, we have to circle back and look at them together at some stage and so we will  
36 certainly do so. Eric.

37 DR. CASSELL: I share Bernie's concern on the one hand, and Larry's  
38 concern on the other hand. Why should it be easier for somebody to consent at this stage  
39 than it would be if they were right there and competent? It doesn't make sense to me.

1 On the other hand the need for the kind of research, moving that forward, is really there.  
2 For myself, I see a mechanism of making this more public. I think the secretary  
3 mechanism is clumsy and people will shy away from it. But there are such things as  
4 registries. Every time an IRB does something like this it goes into a national registry of  
5 research protocols that have been handled this way so people begin to get a chance to  
6 see what actually is transpiring and see what happened with them. I'm not sure how you  
7 get into that yet but I think we can walk ourselves there because I'm convinced also by  
8 the testimony and by my own experience. But we have to find a way to get some of this  
9 to go forward without it being licensed injured.

10 MR. HOLTZMAN: To your part, Bernie, and you know from our  
11 discussions that I share a lot of your sentiments, the concern, I think, is with the  
12 mechanisms down in the lower right hand corner of the no box. Okay? I think we all  
13 agree that the number of people giving broad-based prospective consent or narrow-based  
14 prospective consent is probably pretty small. So that's kind of, at least for myself, very  
15 simple-minded; I like to try to keep certain concepts clean. I think informed consent has  
16 a very important role in being kept robust and clean and that is why, with Larry, I would  
17 like to keep it consistent with our concepts of informed consent but then deal with the  
18 issue below in the lower right.

19 DR. LO: Well, then I think it's, a number of us have said throughout  
20 the day, it becomes crucial how we deal with that issue since you extended that—I mean,  
21 I agree with Larry and Eric. I would like to find a feasible, pragmatic way to allow these  
22 stages to continue and also protect subjects.

23 DR. SHAPIRO: Let me make a suggestion now in view of where this  
24 discussion has gone. Let's turn, without having resolved this or indicating any full  
25 acceptance of it, although I think myself it is extremely useful, let's go to 12, which 12,  
26 in this case 13, is just sort of a follow- on of 12, really attempts to deal with that lower  
27 right hand corner however you get into that corner, whether through this mechanism or  
28 some other mechanism. You know the Recommendation 12. First of all, let me say  
29 something about the Common Rule. I don't think we should worry ourselves with. Do  
30 we want to amend the Common Rule or change a subpart of the Common Rule, we need  
31 language that clearly what we're getting others to think about and they'll figure out  
32 what the best way to go at it is whether it's a subpart of the Common Rule, or the  
33 Common Rule, amendment of the Common Rule itself. Let's just put that aside.  
34 Recommendation 12 was designed initially and is designed to try to make this waiver  
35 process something more real in some sense, well used, than has been the case in other  
36 areas where we also have this capacity to sort of appeal to the Secretary of HHS wherein  
37 the current regulations are very seldom used because this procedure is a very difficult but  
38 not impossible process. So it's just as if, almost as if it's not there. And this original  
39 recommendation here was to try to make that more available by having OPRR establish a  
40 panel which would adjudicate on these matters on behalf of the Secretary. And also by e-

1 mail we sort of suggested yet another alternative which either could be combined with  
2 this one or replace it altogether and that was the recommendation which I think you all  
3 either have copies of or had copies of, apparently, it's at your places, which essentially  
4 says, and I can't get all the language straight without reading it, but in cases which were  
5 described as compelling regarding the cost, the benefit and risk ratio, that the IRB could  
6 if it engages in public disclosure approve such proposals. And although the way it's  
7 written here, it says, it can see protocol, permit interested individuals in groups to  
8 express their views and then it would publicly sort of indicate what in fact it decided. My  
9 own view was that this was an interesting thing to consider, although now that I look at  
10 this carefully, I would rewrite it somewhat when I think they ought to inform the  
11 sponsor, whoever that is, because they may have an interest in it and that should be  
12 specifically mentioned. But, it's, let's not worry about the exact wording here for the  
13 moment. It is another way of dealing with that lower right hand corner Eric talked about  
14 a moment ago or that Bernie was concerned about. And indeed, it will be possible if it  
15 was your wish to in some sense, give the IRB a choice of what it wanted to do. Those  
16 IRBs who felt comfortable going ahead and approving it and publicly disclosing it and so  
17 on could do so. Those IRBs that for whatever reason they had, didn't want to do that  
18 could use the panel but there are mixes and matches here. There are various alternatives  
19 here. I don't know that I understand myself which would be the best but let's just use  
20 this as a starting point to see what other kinds of ideas come up and what people like and  
21 dislike about all this. Alta.

22 PROF. CHARO: I'd like to speak in favor of a somewhat more liberal  
23 version of 12 in terms of the way the recommendation is written, although the key  
24 elements are in the text. I'd like to speak against 12a. It makes me very uncomfortable  
25 and I would like to recommend finally a third aspect to this which has to do with putting  
26 more meat on the bones of our understandings of minimal risk, which may clarify some  
27 of these debates for people. On 12, the recommendation in the bold type, although it  
28 does not say what is in the text but I think is essentially to its efficiency and its political  
29 legitimacy. I think it's important that we understand that this body that we're  
30 proposing as a standing body not simply be there primarily to be a case-by-case appeal  
31 for particular protocols that don't meet the recommended regulations, but that it  
32 actively see its rule as proactively outlining classes of research, type or whatever we're  
33 doing, particular interventions, particular kinds of studies that are usually appropriate for  
34 an IRB to waive, usually appropriate for an IRB to approve despite these regulations and  
35 issue this guidance to IRBs and move then to the IRBs the day-to-day responsibility for  
36 approving those studies. I don't want to see them just as a single protocol appeal board,  
37 but really much more prospective. And second, not in the bold, is the fact that the  
38 membership of it has to be quite representative on the consuming end, the subject end, as  
39 well as the research community to give it the legitimacy to go ahead and essentially  
40 authorize research on people who can't consent for themselves in situations where  
41 there's no benefit to them.

1 12a, which is basically a mechanism that presumes that enough sunshine  
2 on research will ensure that it's done in a way that is ethically appropriate, concerns me  
3 enormously. First, I'm not convinced that you can actually achieve that degree of  
4 sunshine. We are watching IRBs struggle with it in the emergency research waivers,  
5 which I will remind people waivers that are given only for research that is potentially  
6 beneficial not without any prospect of benefit. Second, most of the people who are going  
7 to be seeing all the details about this research are not people who are personally  
8 implicated. They'll never be at risk of being enrolled in research like this and so don't  
9 necessarily have the kind of self-interest that you need to have to have kind of a full-  
10 flavored evaluation of both the risks and the benefits and whether or not it's justifiable.  
11 And third, to the extent that there is any degree of prejudice against the population of the  
12 mentally ill and in this case, I think I am really specifically talking about the mentally ill  
13 and not impaired decisionmaking people in general. There's a possibility of a great deal  
14 of lack of empathy among people who hear about the research. So, I'm skeptical about  
15 the use of sunshine and politics as a kind of protection against abuse as a mechanism.  
16 Finally, I think an awful lot of the reason why there's a lot of pressure on these  
17 recommendations that are on box 12 is because of our lack of clear understanding about  
18 what constitutes minimal risk and a large, in fact, the vast majority of the examples given  
19 to us so far in research that might be hindered substantially is research that's right on  
20 that borderline. The PET scans and the MRIs and the genetic pedigree studies, the  
21 bladder muscle biopsies and spinal taps. Those were the 5 that we got in a memo today,  
22 and it strikes me that there is good data in the literature on the frequency of adverse  
23 events of every type of each of these things. We know how many people died per  
24 thousand. How many people have permanent disability, temporary disability, etc., and  
25 that it is probably time to start adding some quantification to the notion of minimal risk.  
26 We know that we can have some quantification on daily life risk. I sent an e-mail around  
27 with some of those statistics and as a third matter that I'd like to direct, I'd like to  
28 recommend that OPRR be given the resources to actually try and add some  
29 quantification of the notion of minimal risk and begin to issue some definitive guidance  
30 on whether or not these particular kinds of procedures are usually eligible for minimal  
31 risk with an IRB, of course, always checking that the particular population is not  
32 unusually vulnerable, and maybe find that there are far fewer areas of research that will  
33 be hindered by our proposals than people are speculating because we'd achieve some  
34 clarity here.

35 DR. MIKE: I think this is an area of how we present it is going to be  
36 important. So I would look at that last leg on the right side that says no and really put a  
37 positive emphasis on, not present it the way we do now which it just says no, except you  
38 might appeal to the Secretary. It would say that if there is really no individual either the  
39 prospective participant or his or her legally authorized representative, I feel much more  
40 comfortable that we have a processing place for making those decisions rather than  
41 leaving it up to an individual. So, the way I would present this and say exceptions  
42 allowable by the IRB and not talk about the Secretary but the IRB to follow standards of

1 guidelines or whatever that would be issued at a more national level so there's  
2 consistency so that we can combine all of the suggestions that we've made, including  
3 our registry so that, and it seems to me that we can also have those guidelines include  
4 addressing the notion about those little things that are a minor, I don't know what a  
5 minor increment is but, in the guidelines they could talk about how that notion of a  
6 graduated risk can come into the decision of about how waivers may be made or not  
7 without us getting into this sinkhole of having more than two categories of risk.

8 PROF. CAPRON: I agree with Alta's sense between 12 and 12a. I  
9 agree with her suggestion that this we ought to move forward to put meat on the bones  
10 and I wanted to respond to Bernie's earlier comments because the language in 12 and  
11 on page 142 came out of an e-mail exchange of Alta, Jim and I and one thing we didn't  
12 include there, Bernie, is the willingness to approve a project where one has subjects who  
13 have expressed exactly the kind of generalized preference for contributing to research  
14 knowledge and being involved in certain kinds of studies, something which we just ruled  
15 out as qualifying as consent to a protocol but which, it seems to me, in that review  
16 process of something that ends up facing the no and therefore being in this category 12  
17 where that preference of the subject would be very relevant. And if a protocol were  
18 designed to draw on subjects who had expressed when competent a willingness to be  
19 involved in this kind of research, it seems to me that would be a factor which would  
20 legitimately be taken into account in reaching the determinations, because we do  
21 anticipate both case-by-case determinations and the development of generalized  
22 standards, and I would like to see language to that effect included on page 142 because I  
23 think the point you made is a good one and we shouldn't just be throwing up our hands  
24 and saying that someone who's taken all the trouble to say I want to contribute to this  
25 is someone who is more suitable for that research project than when you don't have  
26 that and you want to honor their wish to make that contribution, it seems to me and that  
27 could be part of this waiver process. But, it's not there now.

28 MS. FLYNN: Can I ask, I'm troubled by all this. It seems to me it's  
29 still enormously bureaucratic and is still very difficult to get these studies done that  
30 we're now recognizing are on the borderline but represent a huge volume of the  
31 significant research that we want to see. Let me pose it this way. I have three generations  
32 of suicide in my family. And let's say that my daughter, who is afflicted with mental  
33 illness, has long talked to me about the desire to participate in basic studies that would  
34 look at the genetics that may be involved with suicide and she is unable to herself give  
35 consent. I cannot, based upon that general, in my own status as her legally authorized  
36 representative, because there's no benefit to her in these studies of basic science, I  
37 cannot consent to her being a participant in MRIs, in EEGs that we have to go through  
38 this cumbersome procedure that may or may not at some point be parsed out, but I  
39 cannot as her legally authorized representative, knowing what I know, commit her to a  
40 study that does not have direct benefit? Is that what we're saying here? That I would  
41 have to go through either this secretarial panel or some other process in order for her,

1 because the study will not benefit her condition, will benefit the greater good for many  
2 people, including members of her own family potentially, is only minimally of risk greater  
3 than the current standard and involves very commonly done procedures that most people  
4 have no trouble with but because she is unable to consent, I can't consent and we've  
5 got to go through this administrative bureaucratic hurdle that may or may not in itself  
6 work. Something we haven't constructed so we don't know how it's going to  
7 function in the real world. Meanwhile, 10-15 percent of all people with her diagnosis  
8 commit suicide and we don't know why.

9 MS. KRAMER: When we broke for lunch, Alta and I exchanged some  
10 conversation really a propos of some of the public testimony that was presented and  
11 what became apparent to me was that Alta's understanding of what constitutes "does  
12 not offer the prospect of direct medical benefit" to the subject is a great deal more  
13 liberal, where she sees that as a more open category than I had perceived it to be,  
14 doesn't make any difference. My question is this. I would like to hear a description of  
15 what kinds of research do not offer direct medical benefit. We were having the  
16 conversation as I said, a propos of some of the testimony that was presented, particularly  
17 by the two mothers of young children and I think also by Mr. McNulty and my  
18 perception was that what they were talking about would fall into the category of does  
19 not offer the prospect of direct medical benefit and yet Alta, if I understood her  
20 correctly, was saying to me that there was nothing that they talked about that in fact  
21 would be in that category. That everything they talked about would offer the prospect of  
22 direct medical benefit. So it may be that a part of the problem that we're having here is  
23 that we're not all talking about the same thing so I would like to ask about some  
24 discussion or definition of what that is.

25 PROF. CHARO: My understanding of prospective direct medical benefit  
26 is that any possibility of personalized medical benefit qualifies. That nobody who  
27 testified, in fact, I was referring to people testifying to a particular study that they  
28 wanted to be enrolled in or had been enrolled in, nobody was talking about the studies  
29 that are purely informational such as the imaging studies that can offer no possibility of  
30 personal benefit to the person who undergoes it. They are purely informational. A drug  
31 study, for example, that has a placebo arm means that there is a 50 percent chance  
32 you're not going to get any active drug at all. That is still a study that, in the IRB  
33 world, is one that offers the prospect of direct medical benefit even though your odds of  
34 getting the study drug were only 50 percent and the odds of the study drug will be  
35 helpful are as yet somewhat unknown. That still qualifies for prospective benefit.

36 MS. KRAMER: Well what about the case that Laurie just raised about  
37 suicide?

38 PROF. CHARO: No. Laurie was talking about imaging studies, which  
39 may or may not be minimal risk. No, I'm sorry, genetic studies which some IRBs

1 continually interpret as being greater than minimal risk and others do not and which can  
2 be constructive with lots of confidentiality safeguards. And so again, it's in this, in some  
3 ways the problem is really not about, the problem is not entirely about the  
4 recommendation to be protective in greater than minimal risk research. The problem is  
5 tightly tied to variable definitions of what appropriately belongs in the category of  
6 minimal risk research to begin with.

7 MS. KRAMER: No, no. But I'm asking you about that particular study,  
8 where in the context does not offer the prospect of direct medical benefit to the subject.

9 PROF. CHARO: Well, it depends on the study. If they're going to tell  
10 her something that might affect her future care, it offers the prospect of benefit. If this  
11 was a study that actually could help her, know if she's got a gene that's now highly  
12 associated with particular kinds of conditions and it could affect the way in which her  
13 own medical care is organized, it would offer the prospect a benefit.

14 MR. HOLTZMAN: But if it was the original study to try to find the gene  
15 there's no direct medical benefit.

16 MS. CHARO: If it's the original gene they're trying to find, there's no  
17 possibility of benefit in the foreseeable future.

18 MS. KRAMER: Laurie says that she comes from a family where for  
19 three generations there are instances of suicide so it's highly suspicious that there might  
20 be some genetic correlation. Now, if in fact, if you assume that there may be a genetic  
21 correlation, then can't you say there is a potential for direct medical benefit to her  
22 daughter from being enrolled in that study?

23 PROF. CAPRON: Depends on where in the sequence of research  
24 findings you are. If you're just looking—

25 DR. SHAPIRO: That question remains on the table. We'll get to that  
26 issue but there are others who want to speak also. Eric. I don't know if it's in response  
27 to this or not.

28 DR. CASSELL: This actually sounds like a discussion in an IRB as  
29 somebody tries to move a study from an impossible place to a possible place. We would  
30 really prefer that that solution is not the solution to the project in the same way as  
31 deciding oh, it has no risk, thus moving the study to another place to allow it to go  
32 forward which is what presently happens. We suffer from a couple of things. One is that  
33 we have no information about what happens in this set of sites. How many are out there?  
34 What's going on out there and so forth? That's why I think that whatever mechanism  
35 we come to, there should be a registry. Medicine is full of registries and they work very



1 well. We have tumor registries and special case registries. They're very common things  
2 for us and then at the end of the year you've got some information about what are the  
3 kind of cases that people are seeing. But I also feel that what Laurie's saying is correct.  
4 I think, it's not a question of feeling. I think what Laurie is saying is correct. There  
5 ought to be a way for that study to go forward and yes, she ought to be the one to  
6 consent. On the other hand, you know very well, we can take and change the situation a  
7 little bit and you move think that that parent should consent because you will feel that  
8 that's too much danger involved in that and not enough benefit to anybody but the  
9 parent. So, that, that's what our situation is and even if we want to do these kinds of  
10 studies, you who want to do these kind of studies, have got to find a way that does not  
11 make it so cumbersome, it's moved by going up to the Secretary. That will make it  
12 minimal risk and so forth. You've got to find a way that makes it possible to move  
13 forward but isn't quite so cumbersome.

14 MS. FLYNN: I was going to say, I think that we've made a lot of this  
15 problem by using only the two categories and not defining well what's minimal risk and  
16 so if we're going to stay with the two categories, I understand you wanting to stay  
17 within those two categories, then what are we going to do about much of this basic  
18 neuroscience that is so crucial for all of these brain disorders, all of these people we've  
19 heard. Certainly folks that I deal with see this research as critical and we've gotten  
20 ourselves that it's now special case to do what our, you know, some of the most  
21 significant and in some cases, largest studies going on.

22 PROF. CAPRON: Well, I think we do have an experience in this area  
23 and it is the recombinant DNA advisory committee which reviewed and gave advice to  
24 the director on protocols involving the use of a common DNA first in plants and animals  
25 and then eventually in human beings. And that process, although more cumbersome than  
26 just having things reviewed by the local IRB, was not a roadblock. This is an area which,  
27 in the view of some scientists, has moved further than the science justifies it having  
28 moved. And having sat for a dozen or so years on that body, I will tell you that a lot of  
29 protocols came through which were much much better by the time they had been  
30 through that process than when they were approved by an IRB to the point that some of  
31 them, it was hair-raising to think that the IRB had ever approved them. So, I think that  
32 the sense that this body is a roadblock rather than a channel is a misdescription. We can  
33 count on it doing things and as described in the commentary on page 142, it is intended  
34 that it will through a process, Eric was talking about it as a registry, well everything that  
35 comes before this IRB becomes part, as it were, of a registry, develop generalizations.  
36 And again, we have that experience with the advisory committee. It got to the point of  
37 saying these things, we don't have to look at. We know that they can be done with an  
38 acceptable level of risk without having specific review. We'll review the next one that  
39 comes along that does something new where there's a question about is this too risky  
40 or not. And it may turn out, Laurie, that with that experience, this body will be able to  
41 say, MRI scans for people with these kinds of diagnoses are not more than minimal risk

1 and they do not then, just not on an ad hoc basis that this IRB struggling to give the  
2 researcher a good day, says yes and this IRB says no, but rather that a standard is  
3 established that says that this is or isn't in that category for certain kinds of patients. So  
4 I really don't think we should see this as the National Bioethics Advisory Commission  
5 is saying you can't do huge areas of research and we're establishing a bureaucratic  
6 roadblock.

7 DR. CASSELL: Then we have to make that clear, don't you think? I  
8 believe we have to make it clear.

9 DR. SHAPIRO: Steve and then Jim and then Bernie.

10 MR. HOLTZMAN: One question and one comment. The question to  
11 Laurie. When you were reciting your case, there were two elements. One was that your  
12 daughter asserted an interest in the research and then the second was that in your belief it  
13 was really not, there was not significant risk involved. Was your daughter's assertion of  
14 an interest really the central feature in your case because it goes back to the issue of the  
15 nature of that wish and how that plays out or was it really that there was potential great  
16 benefit for understanding the disease and the research and there was minimal risk?

17 MS. FLYNN: It's hard for me to put a value on one or the other. It  
18 certainly, in this case, would be a combination but were she never to have expressed a  
19 particular view about the research or just to never had that conversation. My view is that  
20 so much of what's necessary here is not really of great risk and in fact, we know that  
21 there are lots of folks who are more than willing to accept these risks that we're putting  
22 in so much protection here, we're not going to get a lot of research and it's basic  
23 science. It's not going to offer a direct benefit. It's not highly risky and we have lots of  
24 people now who are indicating a willingness to participate in it but now it seems to me  
25 that we are suddenly seeing it as an area of potential real concern and requires this  
26 special elevation to a separate panel. I don't understand the need for that.

27 DR. SHAPIRO: Thank you. I have Jim, Bernie, Alta and I have some  
28 suggestions here also.

29 DR. CHILDRESS: I'd like to speak in favor of the proposal that Alta  
30 made with Alex's elaboration. I think it's the direction to go. It keeps some of our, and  
31 Steve's, now I'm speaking specifically of how to handle what here, here's the no, but  
32 be studied in obviously a more positive way. I think this does have the advantage of  
33 keeping a particular concept of consent that would work with them on the other side,  
34 very, very clear, protecting it, but keeping also, certain values simple to our whole  
35 discussion and assessment of protocols while allowing some very important research to  
36 go forward. And I think the kinds of directions that have been proposed in building on  
37 Alta's statement, would permit us to do that and I appreciate the concerns that

1 Laurieps expressed but I think that given the kinds of modifications that have been  
2 proposed and what the panel would do and given the experience, I didn't serve as long  
3 on the RAC as Alex did, but my experience was very consistent with his. I think we're  
4 sort of overstating the barrier. Yes, there is a hurdle to be jumped over but that doesn't  
5 mean that it's going to be set so high that it would create problems for very important  
6 research to go forward.

7 DR. LO: I guess I still have concerns about the OPRR or Secretary of  
8 HHS alternative. I think that the RAC was a very special set of circumstances. We're  
9 talking about type of research that was new, unprecedented, and a lot of concerns about  
10 the unknown. A lot of symbolic concerns, a lot of concerns about long-term  
11 unanticipated side effects. Relatively few proposals, at least in the early stages to my  
12 understanding, were being proposed because the science wasn't really there. And, you  
13 know, I think, my hat has always been off to those of you who have served on the RAC  
14 and really did a lot to sort of clarify the issues and establish a standard of care and really,  
15 as Alex, pointed out, strengthened a lot of the protocols in terms of making them better  
16 science and better ethics. I think, I'm talking about, I think, a different set of issues  
17 here. We're talking about interventions that are commonly used in clinical practice  
18 where there isn't a whole lot more of anticipate. I try to ask a lot of our  
19 neuroradiologists, what's the data on the risk of PET scans and MRI scans in terms of  
20 anxiety, long-term headaches? Is it more or less, are these side effects more or less  
21 prevalent in people with various conditions? We don't know. We have a lot of opinion.  
22 But, these are things that are done a lot and radiologists have standard safeguards. I  
23 think that, you know, I come from the West Coast, to come to Washington for a  
24 meeting—if I had a graduate student fellow who wanted to do a project, no matter how  
25 good the science, that project would not get done if we had to come to Washington to  
26 come to a meeting. I agree with the idea, what Eric said, that we need standards, a  
27 common understanding. We need a registry. We need to develop a sense of what really  
28 ought to be approved most of the time and what's really very different. But I just think  
29 that to have a committee that meets in Washington, that's hard to get to, and you have to  
30 schedule it in advance does present problems when you have a high volume of protocols  
31 that want to come before it.

32 One of the things I like very much about 12(a) is where we talk about a  
33 ratio of benefit to risk, the project is of exceptional importance. We're starting, it seems  
34 to me, to sort of get a sense that of all of the studies out there that are greater than  
35 minimal risk, there are some that we feel differently about than others. Alta keeps talking  
36 about we're close to the line. If we can try and define what those are, that's fine. I'm a  
37 little concerned, frankly, that we're going to end up calling things minimal risk that I'm  
38 not sure are minimal risk. Does any degree of radiation take you out of the minimal risk  
39 category? Those are the kinds of questions we want to get to.

40 But there are a lot of IRBs and people who say that's different than

1 everyday experience, even if the absolute numbers are the same, that qualitative nature of  
2 the risk is different. So I think we're taking a concept that is based on everyday  
3 experience, which is amorphous and then we're trying to use it as a sort of branch point  
4 for regulatory provisions. I'm just afraid we're going to end up with some decisions and a  
5 whole class of cases that just sort of goes against intuition. So 12 I have real concerns  
6 about.

7 I like the idea of bringing together a panel to sort of take the data that's  
8 known, look at the protocols, obviously, look, here's a group that we think really IRBs  
9 should be able to approve, and here's a group that we'd be very disturbed if they  
10 approved that a lot. 12(a), it seems to me, gives some local flexibility. I'd like to hear  
11 more discussion as to whether (a) people think this would be effective, that is the local  
12 IRBs plus sunshine, and (b) given that we now have not just recommended but urged in  
13 regulation there be two IRB members who represent persons and families with a mental  
14 disorder, whether that change in the IRB goes some way towards addressing some of the  
15 issues that 12(a) is meant to address.

16 I actually have some concerns about the publicity. When you have  
17 sunshine, there's both good publicity and bad publicity. Are we going to get more  
18 thoughtful discussion, or are we going to get more sort of newsworthy drama? And I'm  
19 not sure.

20 DR. SHAPIRO: Let me just interrupt here because I find an unusual  
21 situation. I have my own perspective on this that may be somewhat different than at least  
22 the combinations I'm hearing here. I'd like to just be talked out of where my head was on  
23 this because probably I just haven't seen this carefully enough.

24 First of all, if I look down this tree, which I find extremely helpful, I'm not  
25 as worried as Steve, I'll use your name but it means for your group, I don't mean to  
26 attach this to you, I'm not as worried when I get to the prospective consent to protocol  
27 as keeping, as it was put, the kind of integrity of the idea of consent. We're already down  
28 a branch where consent is not possible. We're dealing with people incapable of giving  
29 consent. And that's why I had thought that, as 11 indicated, and as you indicated  
30 somewhat actually in your own kind of musing about this, that there might be some  
31 possibility here to talk about types of research or classes of research that one could have  
32 some prospective consent, although we might want to invent some other word other  
33 than consent, because that would allow more cases to go down to the "Yes, LAR  
34 monitor."

35 So it's not like you just do it and that's the end of it. You have a legally  
36 authorized representative monitoring in the best interests, as we say down here, et  
37 cetera, et cetera. So it seems to me, my own view is that there at least is some argument  
38 that we ought to allow more cases down to that "Yes, LAR monitor." That's just my

1 own view.

2 With respect to 12, 12(a), et cetera, et cetera, that is 12 being the  
3 Secretary's panel, and I accept the notion that that has to be fleshed out in some way  
4 that's more effective, but the idea of whether public disclosure is a good or a bad idea,  
5 whether that allows for too much IRB flexibility, that is, is that a huge loophole which  
6 some army of people are sort of going to march through in a way that overwhelms the  
7 system. I have I think a rather different view than has been expressed around the table  
8 about that; namely, I believe that public disclosure and public disclosure to sponsor  
9 would be very effective. I know I'm just asserting that and I certainly can't provide you  
10 with a detail. But that means that not only the local IRB has put itself on the line  
11 publicly, but so have the sponsors who if they fail to object. And that's a pretty major  
12 influence for a lot of the research, especially the research that may be financed by the  
13 Federal Government and so on.

14 So it seems to me that while in this period where we're trying now to  
15 struggle with these recommendations and develop some guidelines, this is not something  
16 that's going to be put in concrete and stay that way forever, it will evolve on its own as  
17 we gain experience, that there really was some benefit to allowing some local IRBs some  
18 flexibility in cases that they found compelling. I chose the word compelling in that thing  
19 because that meant a lot to me. I understand everybody has a different view of what  
20 compelling means, but I meant that this was something which they believed to be  
21 important. And if they decide to go ahead, if anybody objects, they've got to be able to  
22 explain that compelling to somebody at some stage.

23 I thought if you took some combination, I understand it's not well  
24 articulated here, what is 12 fleshed out and 12(a), allowing IRBs to perhaps choose, as I  
25 said before, amongst these paths that you could either describe this as allowing more  
26 thoughtful flexibility or as allowing a huge loophole through which some people are  
27 marching inappropriately; that is, doing things which we would all think inappropriate.

28 Now all of that says that you believe that with the guidance we've  
29 provided that the IRBs at the local level will be doing their job well. I understand that. It  
30 puts some faith there and time will tell, if we ever recommended that, time would tell  
31 whether that faith was justified or unjustified.

32 Given that, if these recommendations go forward, whatever we choose in  
33 this area, we will have substantial new guidelines in place for IRBs to deal with in this  
34 area. It's not like it depends only on any one of these recommendations. And that that  
35 made some sense.

36 So I have two concerns. One of which is I think we share, that is we want  
37 this "No" to be not just no, but some process which is believable, and I believe in some

1 flexibility in that process and I'd like to provide some flexibility and experimentation in  
2 that process. And I also believe we want more, I would allow more to go under the  
3 "Yes, LAR monitor" than I think seems to be the general feeling. It seems to me to not  
4 allow that means, and I understand this is an open issue, it really depends on how much  
5 you think you can rely on the IRBs to do their work. That's what it comes down to in my  
6 view. And I understand that we don't have an answer to that.

7 Alex?

8 PROF. CAPRON: I guess I would ask you, you say you have no  
9 evidence, and you almost started to say you have no detailed evidence and you realized  
10 you have no evidence, it's supposition. But on the other hand, given the recent studies of  
11 IRBs, given OPRR's report on UCLA's IRB, OPRR's report on Maryland, two of the  
12 most distinguished psychiatric institutions in the Nation, what basis would we have for  
13 thinking that giving the IRB more discretion is going to lead to more defensible results?

14 DR. SHAPIRO: That comes down, the way I think about it, to whether  
15 we think this public disclosure or LAR monitoring means anything or not. Maybe I'm  
16 wrong, but it seemed to me that those were meaningful things. If they're not, then, of  
17 course, it's an empty gesture.

18 PROF. CAPRON: I think the LAR monitoring is a useful adjunct if you're  
19 dealing with a situation in which the person has consented previously and you still want  
20 to make sure someone who is competent is watching out for their interests, or in which  
21 you have a prospect of benefit and again you want to be able to get the person enrolled.

22 DR. SHAPIRO: The prospect of benefit doesn't—I agree with that.

23 Either of those uses of the LAR I'm comfortable with. But the IRB, in  
24 many cities an IRB could run in the local newspaper or something a little announcement  
25 that it has approved a final protocol. Why would that generate a great deal of attention  
26 from anybody?

27 DR. SHAPIRO: My own view is if both the sponsor and the public know  
28 that interested parties will, if they're interested, take advantage of the information that's  
29 available. That's just my own.

30 Arturo, you've been waiting a long time, then Eric, then Alta.

31 DR. BRITO: What I have to say goes along with what you just said.  
32 What would be wrong, going back to what Laurie's concern is, going down to the "No  
33 LAR" on the right, why can't that divide up in two arms? There may be, I'm sure there  
34 are plenty of situations where there may be no prospective benefit, there was no

1 prospective consent, but the LAR may go ahead and approve and might have  
2 justification for approving; for instance, your daughter giving previous approval or  
3 wishes to be involved in something like this. So we're trusting the LAR to be protecting  
4 that individual. We've already come to that conclusion in those situations, right? So why  
5 can't we trust LAR to say, okay, even though this study is greater than minimal  
6 risk—that's another point I was going to make before, I still think that's very subjective,  
7 going along with something Bernie was saying—but greater than minimal risk because  
8 they're going to get an MRI, but I feel it is worth taking this risk because my daughter  
9 previously told me that she would want to be involved in this study. I just think that if  
10 there is justification for LAR, we should honor that. I just think there's other possibilities  
11 here, going along with what you just said.

12           Going back to what Alta said a while back, I think a big part of this  
13 problem is the quantification or standardization of what minimal risk really is. I still  
14 believe though that we need to keep the two-tiered system greater than minimal risk and  
15 minimal risk, because I feel that it's always going to be very difficult to quantify things in  
16 that sense. But I think that we also need to make it very clear that there need to be  
17 standards in research. For instance, what I'm hearing in MRI, when I heard Tom say that  
18 and I asked some people from NAMI during the lunch break about this, why isn't MRI  
19 considered more than minimal risk or greater than minimal risk in someone with mental  
20 illness? What scientific proof is there of that? And I think that's the problem, there's a lot  
21 of subjectivity with IRBs individually determining what is minimal risk and what is not. I  
22 don't think it's a problem with the number of tiers, I just think it has to do with specific  
23 tests.

24           DR. SHAPIRO: Eric, and then Alta.

25           DR. CASSELL: I changed the recommendation to 12 somewhat to say  
26 "protocols involving greater than minimal risk but no benefit to the subject, where an  
27 LAR monitor exists should be reviewed by a local IRB. If the benefit in terms of  
28 knowledge is sufficient to balance the risk, the IRB should approve the protocol so that  
29 it might move to a special panel of OPRR for final approval."

30           So let the IRB deal with the weight of it, get all the simple issues  
31 resolved, and then if that's what it is, then let it move on to this special panel and get a  
32 final approval there. I also don't think that the public light in this sense does anything.

33           DR. SHAPIRO: Okay. Alta.

34           PROF. CHARO: I'd like to address a couple of things that came up  
35 particularly in Laurie and Harold's comments. I think that the governing ethic with which  
36 we approach research in the United States is not one of a kind of communal benefit and  
37 communal obligation. We could develop that. We could say as a matter of

1 intergenerational justice, I benefitted from research on other people, therefore I should  
2 be drafted into research and it will benefit the next generation. But that's not the way  
3 we've chosen to go, although I think it's entirely defensible in some ways to make that  
4 argument. We go for a very individualistic look and we say are people willing to  
5 volunteer individually.

6 Now, one of the things that has frustrated me is in trying to divine the  
7 individual preferences of people who can't speak for themselves. And Laurie, you  
8 asserted at one point that most of these people would like to be in this kind of research,  
9 referring to research that has no benefit to them and which has risk levels that are just  
10 above to someone's specified level above minimal risk, right? Research that poses some  
11 degree of risk. And my question is, how do we know this? You've got anecdotes, I've  
12 got anecdotes. The only thing we really know for sure is that most people don't  
13 volunteer for research, and of those who do, extremely few volunteer for research that  
14 has no personal benefit.

15 So I'd like, number one, to suggest that the recommendations ought to  
16 include an effort to actually find out what people do really want. Because consent is not  
17 an end, it's a means to an end. Consent is a way to find out what people want and  
18 facilitate their choice. If we can find out what they want and facilitate the choice in a way  
19 that doesn't involve traditional informed consent, we do that. And that would mean  
20 trying to understand, and I would challenge some of the people in the mental health  
21 community to work on this kind of research, trying to understand what people say they  
22 would be willing to volunteer for and then double-checking and finding out how much  
23 they actually volunteer for. Because we all I think believe ourselves to be more altruistic  
24 than we actually are when push comes to shove. But you're quite right, this is a special  
25 population. There might be analogies—people with breast cancer who say I'd volunteer  
26 for this kind of non-beneficial research and how many actually do—to get a handle on  
27 understanding what's going on out there.

28 If somebody could persuasively argue that the overwhelming majority of  
29 people who can't consent for themselves in fact want to be enrolled in non-beneficial  
30 research of some magnitude of risk, I think all these recommendations should be  
31 revisited. But I think until we can get that kind of information, you have to presume that  
32 these people are no different than anybody else, which is that a minority of them are  
33 actually willing to offer themselves up as altruistic lambs and we have to try to facilitate  
34 their choice of non-volunteerism.

35 Which is why I'm very comfortable with the way we've gone so far. I'm  
36 moveable on this question about blank check versus narrow consent. But on the bottom  
37 line of whether or not they should be enrolled without consent and why that matters, I  
38 think that you can't evade the kind of fundamental individualism here of facilitating  
39 people's own choices. We're not allowed to just say that it is compelling research and,



1 therefore, we're going to draft you into it no matter how many people vote in favor of it.

2 Finally, and very briefly because I know I've spoken too long, on the 12  
3 and 12(a) thing. I think 12 can be made into something that's highly efficient and does  
4 not require a trip to Washington. Once categories have been announced, IRBs are able to  
5 approve the protocols right there locally. They don't have to send somebody to  
6 Washington. On 12(a) with sunshine, not only does it bother me in terms of  
7 implementation, but I think that, again as a matter of individual rights, no matter how  
8 many people agree politically out there in the sunshine that it's okay to draft me into  
9 research that you find compelling, I find as a matter of principle that it's wrong for you to  
10 be allowed to draft me because they all think it's a great idea. And so it's a matter of  
11 principle as well as pragmatics that makes me uncomfortable with that particular  
12 recommendation.

13 DR. SHAPIRO: Diane.

14 DR. SCOTT-JONES: I think the comment about our definition of  
15 minimal risk, it seems that a lot of the discussion has centered on what procedures  
16 belong in the category of minimal risk and what procedures then belong in the category  
17 of greater than minimal risk. I think there are other ways of looking at how to label  
18 particular studies minimal risk or greater than minimal risk. I think we have a very good  
19 discussion of that on page 132, which actually comes under Recommendation 5, where  
20 we talk about the importance of looking at the risk categories in context and that a given  
21 procedure may not necessarily be risky for all persons in all ways of administering that  
22 procedure. So there's very good discussion here of how say a venipuncture might be  
23 disturbing to some people who have limited understanding of what is being done to them  
24 when they undergo that procedure.

25 I don't know how we can write it into our specific recommendations here,  
26 but some way we ought to get away from the idea that we can create a listing of  
27 procedures and call those minimal risk and another listing and call those greater than  
28 minimal risk, because over time those procedures will very likely change and new ones  
29 will come into existence. So I very strongly favor something that is more contextual,  
30 which will require that IRBs and investigators use good judgment and good rationale for  
31 whether they have a minimal risk study or a greater than minimal risk. I really think we  
32 should get away from the idea of cataloguing procedures as one or the other.

33 DR. SHAPIRO: The area where we are having great difficulty right now  
34 is the greater than minimal risk/no prospective benefit. I haven't heard so far at least,  
35 maybe that will come up, any compelling argument that something like writing  
36 recommendations around this tree, taking advantage of other comments that have been  
37 made here, would present us any insurmountable difficulty except in the area called "No"  
38 here, the final no here, which I think we all agree shouldn't be left like that. The question

1 is, what set of procedures would we allow to take place once you're in that "No"  
2 category?

3 We have the recommendation, which can be fleshed out in response to  
4 some of the interesting ideas here, of making something workable out of what we loosely  
5 call the Secretary's Panel. Maybe the first step would be to stop calling it the Secretary's  
6 Panel because that sounds by itself so ominous that it's not likely, in my view, that we're  
7 going to get it. But maybe we can think of some procedure which is national in scope  
8 and yet is not at a level where it just will never be used, because I don't think anyone has  
9 expressed that prospective. In addition, that that will also be the source of guidance as  
10 we go along as to how IRBs should behave. So it's a kind of two-way street is what I  
11 understand people to favor here. But I haven't heard anything else. I don't see much  
12 support, for understandable reasons, for anything else right now.

13 Bernie?

14 DR. LO: It would help me if we distinguished a lot of ideas that have  
15 been combined here. I heard some people say that the IRB should have some discretion  
16 and then other things might happen. So one proposal was someone ought to require an  
17 additional layer of review on top of that IRB, some sort of panel that would be  
18 empowered to look on a case-by-case basis at these other protocols that the local IRB  
19 approved. The second proposal was that a panel be convened to try and draw broad  
20 categories of guidance for local IRBs to apply. The implication being that if we could set  
21 some standards here, IRBs would be on surer ground and we wouldn't have to provide  
22 as much extra scrutiny of individual protocols. And then there was an idea which is  
23 somehow getting a handle on the combined experience of IRBs. Eric talked of a registry.  
24 Harold talked about a public disclosure of protocols the IRB was approving. The idea I  
25 think would be that somebody could then go back and say let's look at all the proposals  
26 of this ilk that the IRBs around the country have approved in the last year and analyze  
27 them and see whether it makes sense, whether there are patterns emerging, where there  
28 are danger spots that no one was aware of.

29 It seems to me those can all be separated out. I'd like to maybe encourage  
30 us to think of each of those separately.

31 DR. SHAPIRO: Bernie, I think that's helpful because I think you're quite  
32 correct to say that all three of those ideas have been around and suggested here. But  
33 what would you think, if we were to flesh out a recommendation like this, and I don't  
34 have the words right now, for really a single panel of some kind doing all three of those  
35 things, because that's where the information will be coming to, that's where the  
36 discussions will be taking place, that's where the case-by-case evaluations will be taking  
37 place, and you'll build up some knowledge over time. The idea being that this is not just  
38 a panel that says yes and no, but it's a panel that actually develops ideas which are helpful

1 to local IRBs and would have as its charge that it really should do this because it wants  
2 to shed itself of some of these responsibilities over time if evidence and experience  
3 indicates that that's appropriate.

4 But I think the three ideas you have are all genuine and all important.

5 DR. LO: In some sense, the RAC did that, right?

6 DR. SHAPIRO: Yes.

7 DR. LO: The RAC both reviewed individual protocols and then  
8 developed some general guidance.

9 DR. SHAPIRO: Correct.

10 DR. LO: I guess my concern is the pace at which centralized "blue  
11 ribbon" committees work. This is going to be a committee that people are going to do on  
12 top of everything else. It's going to take a long time to develop these general guidelines.  
13 I'd like in the meanwhile while that's being done to have some process that provides  
14 some balance between gathering information on what's really going on out there but  
15 allowing things to proceed at a reasonably good pace. I just am a little skeptical that one  
16 central committee is going to be looking at all of the protocols from around the country  
17 that fit into this "No" block. That's a lot of protocols.

18 PROF. CAPRON: Don't generalize on the pace issue from the experience  
19 of this Commission.

20 DR. CASSELL: I think that's why the local IRB should see it first so that  
21 it screens it out and you don't have everything going up there. You have the local IRB  
22 handling the first look.

23 DR. MIIKE: Bernie, it can be a live process where you have some central  
24 body set up some interim guidelines by which IRBs then begin to work. Meanwhile, that  
25 central body does all the other things and revises the recommendations.

26 DR. LO: Then I'd like having some sort of first-cut at guidelines going to  
27 IRBs, saying this is what we'd like you to work with, for the next six months we're going  
28 to monitor you, we want you to come back and tell us what the problems are, what  
29 works, what doesn't, we're going to review everything you approved or some sample.  
30 That makes more sense to me. Someone would have to work out the numbers of  
31 protocols that would be coming—

32 DR. MIIKE: Remember, I came into this with Laurie saying we should

1 have approval by an LAR whether or not there was benefit or not even on greater than  
2 minimal risk I have been persuaded that we need to distinguish between the two sides. I  
3 think that if much of that decision can be held at the IRB level, it is just another thing for  
4 the IRB to consider rather than another step aside. So that an investigator brings a  
5 protocol in and says, "By the way, we have subjects here that were not able to give  
6 permission and it's greater than minimal risk," and it slots that into another category in  
7 which the IRB can make a decision. But they can make that decision all at the same time.

8 DR. SHAPIRO: Further comments?

9 PROF. CAPRON: Is this a matter on which, as your message to us in  
10 advance said, if there aren't three or four people who really favor 12(a) that you will  
11 simply note a concurring or a dissenting opinion at this point?

12 DR. SHAPIRO: Well, I don't know if we're at that point yet because we  
13 need to flesh out some of these things into actual language. But I think this may be an  
14 issue on which there is sufficient disagreement amongst us so that those who feel  
15 strongly, whatever position the majority of the Commission adopts, others may feel  
16 strongly enough to say something about it, in which case they are certainly welcome to  
17 do so. And as I said in my e-mail to you, while I think the primary benefit of arguing all  
18 these things out is so that we all get a little smarter, but the primary objective is not so  
19 that we all agree to everything. There may be alternative points of view which are worth  
20 surfacing, and that's a benefit also. But I think trying to talk ourselves to consensus has  
21 the value of testing our own ideas and seeing whether we do find some genuine  
22 consensus but I don't want to hide disagreements beyond some superficial consensus.

23 Laurie?

24 MS. FLYNN: Given the choices we have, I certainly like a lot about  
25 what's in 12(a). I believe we need to engage the IRBs in an ongoing process where they  
26 grapple with these issues, where they learn these issues, and where we enable them to  
27 come to understand much more than some of them may what the compelling needs may  
28 be and that some of these studies are really not of great risk.

29 I also think that it's important to recognize that even though we have  
30 tended here, and it is continuously reinforced I think within our process, we tend  
31 naturally to hear, as we should, about cases that are of alleged abuse—we have heard  
32 about a variety of individual stories, we are aware that there is a need for some reform  
33 and some additional safeguards—but we also need to recognize that the vast majority of  
34 the folks out there in the IRB system and the vast majority of folks out there in research  
35 are doing a good job, are wanting to do a stronger job.

36 I think with the work that we've done here and the visibility that our

1 discussions have had, I think that if there was ever a time to really follow in on their  
2 interests, continue to work with them around how to better understand the necessity of  
3 these protocols, this process has set the stage. So I think that it's particularly useful for  
4 us to move in the direction of the flexibility that's outlined in 12(a) and remaining with  
5 the fundamental structure of our system, especially given the other kinds of supports that  
6 we're recommending be put into regulation.

7 DR. SHAPIRO: Trish, excuse me.

8 MS. BACKLAR: I'm going to be going very soon, so that's why I just  
9 wanted to say a few words about this. I think, Laurie, one of the reasons that we talk  
10 about the bad cases is, of course, the bad cases count when people are harmed. As Alex  
11 has said, when we look through protocols, one protocol that harms people is enough.

12 But I just want to say a few words about the Recommendation 12. I  
13 actually really agree with Alta. I'm very concerned about the public comment part. I can't  
14 give you a process of doing this, but I see it as a process that would work backwards and  
15 forwards between a review committee and the IRBs, a kind of secretary that would  
16 review these in such a way as to develop a template for IRBs, a guidance for IRBs.

17 But the public comment I think really won't work. I'm thinking of a class  
18 that I'm teaching right now in bioethics and telling them about the waiver for research  
19 with stroke and how our university in Portland had put advertisements in the newspaper.  
20 Nobody had ever seen them. And then when I showed them the advertisements, they  
21 didn't understand them. It sort of misled them about what was going on. And I think the  
22 IRBs in our city at least have had not very good feedback when they have tried to get  
23 public comment.

24 DR. SHAPIRO: Let me say a word about where I think we are and what  
25 we should do next in order to move this process forward towards completion. Let me  
26 make an observation, however, on this issue of who reads the newspaper. There are, of  
27 course, lots of things like this, including the fact that most surveys haven't the slightest  
28 idea. They know there's a government crisis, they don't know if it's in a surplus or a  
29 deficit or which is the problem, they can talk about it for ten years in the newspaper  
30 every night and people don't know. But people who are interested and care about it do  
31 know and they tend to move the system. And so even though there might be 98 percent  
32 of the people or 99 percent who don't have any concept it was ever revealed, I think  
33 there's still some benefit. But I don't want to press it on because I understand we will  
34 disagree on this.

35 I think that where we are right now is that we ought to provide to the  
36 Commission within the next week or so a revised set of recommendations that go from 8  
37 through what is now, I think, 13 that will build around this tree but it will flesh out a

1 good deal with the so-called "No" lower right-hand corner along the lines that have been  
2 suggested here today. And we'll see how the Commissioners feel about that once we  
3 flesh it out and put language beside it.

4 As we go through this, we will also consider whether there are some  
5 alternatives to consider, which we'll share with you at that time, trying to take as much  
6 advantage of both the comments that have been made today. Because I think there  
7 remain some concerns and some disagreements amongst us that may be unresolvable,  
8 and that's fine. Then we'll have some different opinions reflected in the report. I think  
9 we'll try within the next week or so to get a couple of alternatives in front of you and just  
10 see how we feel about it and decide finally how a majority feels in our next meeting, and  
11 then we'll just go ahead with that.

12 I think we have talked this out long enough. We have to face the fact that  
13 there are allegations on all sides on every issue. There are allegations that there are too  
14 many people that are not treated well. There are allegations it will stop research. There  
15 are allegations here, allegations there. It's very hard when you come down to it to get  
16 any information on any of the allegations on any side of the issue. And so we are faced  
17 with a lack of real data, what normally might try to guide us. So we have to have some  
18 process which develops that more effectively over time and, as Trish said, have some  
19 flexibility in the system.

20 But I think that we've talked about these long enough today. I think we  
21 know where we all stand. We all ought to be thinking about it. And I ask you once again,  
22 if you have thoughts that you can articulate in written form and share, that would help us  
23 as we try to develop this over the next week or so. We don't have to finish it but we have  
24 to get these alternatives in front of you within about a week or so. We'll do this by e-mail  
25 or some other form. And then we'll just see how we respond to that. Because it seems to  
26 me we've said enough on this today, but I don't want to close off further discussion. I  
27 know we're about to lose members who have got planes to make and so on.

28 Laurie?

29 MS. FLYNN: I just have one related point that I think was mentioned and  
30 I do think it's important. We're making some assumptions in the absence of data about  
31 the willingness or lack of willingness of individuals with decisional impairments to  
32 participate in research that may be of greater than minimal risk that does not offer them  
33 direct benefit. We've highlighted that as a problem and we really don't know what the  
34 willingness is of that subject population to accept those risks.

35 As we heard our board member here from our organization this morning  
36 talk about, one of the things we've tried to do and that I think I can flesh out and share  
37 over the next week is we've tried to go out via an admittedly not representative but

1 nonetheless useful e-mail survey to a variety of our members around the country, and we  
2 have a very large membership of people, 85 percent of the membership who have these  
3 significant disorders, to ask them (a) have they ever done such, have they ever  
4 participated in such studies; and (b) would they be interested or willing to. I think our  
5 preliminary results indicate that a lot more than you may think people with these  
6 disorders recognize the value of participating even though there's no direct benefit. And  
7 it might be useful to try to raise some discussion with the subject population about these  
8 issues to begin to bring some data to the discussions over time.

9 DR. SHAPIRO: I'm sure that would be and I'd very much like to share  
10 that information. This is difficult information and evidence to gather, as you appreciate  
11 as well as anybody else. But everything is building towards a better understanding.

12 Diane?

13 DR. SCOTT-JONES: I have three comments that I would like to make  
14 before we break today. One has to do with the regulations regarding children. There  
15 have been references to children in speakers from the public today. My understanding  
16 was that in this report we are not addressing the issue of children's participation in  
17 research because that's covered under separate regulations and those regulations are  
18 somewhat different, especially when it comes to how you categorize risk. And I think we  
19 say that in a footnote in the very first chapter. So I just want to be clear that that is the  
20 case.

21 DR. SHAPIRO: That's an issue some of us have been discussing today,  
22 and if there's a footnote, I don't have it. But the intention is, you're right, this is really  
23 intended for adults. But I think we need some language which would at least recommend  
24 these ideas to those concerned with regulations for children they may wish to consider.

25 DR. SCOTT-JONES: We have a footnote on page 1 of the first chapter  
26 as footnote 1 where we mention the Federal regs that apply to vulnerable populations.  
27 So we do have that and there are other places throughout the report where we do talk  
28 about children.

29 But I have a couple of other—

30 PROF. CAPRON: Could I respond directly to your point and then yield  
31 the floor back to you? I would suggest that on page 117, on lines 4 and 5 we have the  
32 following statement: "In this concluding chapter we summarize our recommendations  
33 and identify the individuals or groups to implement the recommendations." I would  
34 suggest either the next two sentences or a footnote at the following two sentences, "Our  
35 conclusions and recommendations directly address research that may involve adult  
36 patients as subjects in research. Those charged with reviewing and implementing our

1 recommendations should consider whether any need to be modified when applied to  
2 research with children."

3 We cannot go through, Alta convinced me of this during a break, we  
4 cannot go through now and fine tune each of these. But if we alert there that we were  
5 thinking primarily of adults when we were writing this, that I think is the point to drop  
6 that footnote or add those two sentences to the text, whichever, and I will give the staff  
7 that language.

8 DR. SHAPIRO: Laurie?

9 MS. FLYNN: I understand that we are focusing on adults. But what I  
10 heard from these mothers was their youngsters are now not capable, they're not likely to  
11 ever be capable. The role that these families are playing in making decisions, which is a  
12 role based on trust in their caring about the welfare and benefit of their youngster, they  
13 will have that same relationship when that youngster becomes 19 or 21 or whatever.  
14 They will be standing in that same place. They will have done those same things. But  
15 according to the way we're drafting this, they will suddenly have a lot less to do and be  
16 trusted a lot less for kinds of research.

17 DR. SHAPIRO: That's an important point.

18 I want Diane to get to her other comments.

19 DR. SCOTT-JONES: Okay. I have two more points that I want to make.  
20 But in response to what Laurie said, I agree with what Laurie just said, but there's also  
21 the issue that we've been accused pretty directly of stigmatizing the persons who are the  
22 subject of this report. I think to assume that they will be in some sense children, even  
23 though in some ways they will, I think that's demeaning to them more so than we've been  
24 in this report.

25 But my second two points, one has to do with my also listening to the  
26 people who spoke to us from the public today. I was really struck by the possibility that  
27 when people are thinking about participation in research, they are not really governed by  
28 the two concepts that form our analytical frame, and those are risk and benefit, it seems  
29 to me that there's at least one other element, and that's the notion of hope for people who  
30 have been perhaps made to feel hopeless at times about the plight of the persons in their  
31 families. I don't think that people are actually making decisions on the basis of risk and  
32 personal benefit. There is this idea of hope, even if the hope extends a generation away. I  
33 don't know how we can incorporate that into our report at this point, but I believe that  
34 our analytical frame may not represent the frames of mind of persons who are caring for  
35 people with mental illness.



1                   And then my final comment is that I'm very concerned about the strategy  
2 that we have for putting the report together. I know that we don't have time to go  
3 through in detail, but one of my concerns is that reading through chapter 5 and getting  
4 the gist of the recommendations and, more importantly, being able to see them as a set of  
5 recommendations is made extraordinarily difficult by all of the explanations. I believe it  
6 would help to see these recommendations as a set if somehow this chapter could be  
7 organized differently without so much coming between one recommendation and the  
8 next and without the extensive introduction at the beginning which really repeats. I think  
9 it's very important for this report to be as concise and crisp as possible. I just hope that  
10 we can work toward that.

11                   DR. SHAPIRO: Those are very good points. As you know from what I  
12 told you before, any specific recommendations we'd be glad to look at. We need all the  
13 help we can get. So please let us know.

14                   Alex?

15                   PROF. CAPRON; You said we're going to be looking at 8 to 13 again. I  
16 wanted before leaving to offer the following language for 8 and 10, it doesn't seem to me  
17 they have to differ, and I will leave it with you but I'll read it out.

18                   Recommendation 8. "An IRB may approve protocols in this category of  
19 research with subjects who are capable of making a decision about participation provided  
20 that informed consent to participate will be obtained before a potential subject is enrolled  
21 in the study." Isn't that a straightforward way?

22                   And it seems to me it applies for 10, which is the other category of  
23 research but the same thing as if you have a capable. I'll leave you that language.

24                   DR. SHAPIRO: Okay. Yes, Steve?

25                   MR. HOLTZMAN: While we just have the people still here, a sense of  
26 the Commission. I feel like we've gotten ourselves in a box. What I mean by that is, at  
27 least I'll speak for myself and test it on others, when I look at the protocols which spur  
28 me to want to erect the protections, particularly down in the right-hand corner, and then  
29 I look at the protocols about which people are concerned that we're throwing the baby  
30 out with the bath water, there's no overlap in those protocols whatsoever. So if others  
31 share that sense, how do we get ourselves in that position?

32                   PROF. CAPRON: Well, I don't think that's true.

33                   DR. SHAPIRO: And I don't share that sense.

1 MR. HOLTZMAN: You don't? So that when one looks at the kinds of  
2 protocols where people are saying I'm very concerned that a PET scan will be defined as  
3 more than minimal risk even though, that's going to be—

4 DR. SHAPIRO: The issue to me is not whether something is more than  
5 minimal risk or not. The question is what's the appropriate level of protections for any  
6 particular protocol. And we're just saying that once it goes over minimal risk, there are  
7 certain things that are required. Other things may be put in, but certain things are  
8 required.

9 Now we tend to get in the cases before us extreme examples. So, yes,  
10 they are far apart. But I think the problems don't go away, the fact that there's a  
11 spectrum of issues to deal with and there's a spectrum of protections to deal with. And  
12 what this says is if it's greater than minimal risk, there are certain requirements; they  
13 aren't all the requirements, they're just some of them, but these are required for  
14 everything above minimal risk. But within the greater than minimal risk categories there  
15 are all kinds of protocols, some with much more risk than others, and you wouldn't want  
16 to see the same protections in every single one of them. That's what an IRB is for and  
17 that's what investigators are for is to understand just yes, there are certain requirements  
18 that come in that they get by getting greater than minimal risk, but then there's a huge  
19 category of research in here and the local IRBs have to decide what set of protections to  
20 wield in this case.

21 But I do think there's a problem with this and we're going to have two  
22 alternatives in front of us, I hope, by the time next week rolls around, one of which some  
23 of us I think will consider as being too lenient and others won't. And we're going to have  
24 to decide just which way we want to go. And in my mind, it really is a question of how  
25 many protocols are you going to get down the right-hand side of this page, not only the  
26 lower right, but the upper right part of this page. I think there are good arguments on  
27 various sides here, but we're just going to have to decide which are the most convincing.

28 When we send out these to you, please, some of you are very active  
29 participants in this e-mail and others are not. If you really want to have an impact on  
30 what our choices are going to be at our next meeting, we have to hear from you because  
31 we really want to be responsive and I want to put something in front of you that is fair  
32 and reflects your perspectives on things, although in this area we have different  
33 perspectives and there's likely to be at least two proposals.

34 DR. BRITO: Since we spent so much time on the bottom right-hand  
35 corner, can we go back up to line 7 for a clarification? Maybe Steve or somebody else in  
36 that group. When we put LAR monitor under the "Yes" on the top right there, how does  
37 that differ from "LAR approves." This means it's just the LAR understands the fact and  
38 just makes sure everything is going along okay and there's no other procedure?

1 MR. HOLTZMAN: It was meant to reflect what's in 11(c), I believe.

2 DR. CHILDRESS: Continuing or withdrawing would be the key—

3 DR. SHAPIRO: Yes, that's what it is.

4 DR. BRITO: Okay. My question becomes then, going back to the  
5 prospective consent to I guess we're talking about a specific protocol, I'm not sure we  
6 came to agreement on that, but a specific protocol, what happens if the protocol changes  
7 but doesn't change where you increase the risk anymore than it started? For instance,  
8 there's some modification or something, does it still go to the "No" and therefore you  
9 pose a question for prospective benefit, or does it go to the "Yes?"

10 DR. SHAPIRO: I understood, although Steve had some ambivalence on  
11 this, I think it's fair to say, I think most members of the Committee said they thought of  
12 that as parallel to the informed consent and then you dealt with a particular protocol. I'm  
13 not trying to defend that, I'm just trying to describe it.

14 MR. HOLTZMAN: Okay. And so if you change the protocol, there  
15 would be a new consent involved.

16 DR. BRITO: There may be a point here where you don't have to get to  
17 the question of prospective benefit. If the protocol changes, just some minor  
18 modifications where the modifications are all at minimal risk, then maybe this is one of  
19 the exceptions where you don't need to go and ask the question about prospective  
20 benefit.

21 DR. SHAPIRO: That's an interesting idea. This is all greater than minimal  
22 risk. What you're saying is if you look at the changes in the protocol and they're all  
23 minimal risk changes, that is as added or subtracted or something are all sort of minimal  
24 risk procedures, wouldn't that be adequate?

25 DR. BRITO: And that might minimize how many things go down to the  
26 bottom right-hand corner.

27 MR. HOLTZMAN: I actually think, and I don't know if we have any  
28 data, but the number of prospective consents that are in play compared to the amount of  
29 research we're talking about is vanishingly small. So noodling around in this particular  
30 area I don't think has a tremendous impact. It has a symbolic impact and maybe a  
31 meaningful impact if you think that autonomy is the critical issue and the most important  
32 and dominating issue.

33 DR. SHAPIRO: It's also true that there's a dynamic going on here if new

1 regulations are adopted at some stage that people start behaving differently. But I think  
2 we understand these issues. I don't think we can profit more by this afternoon. We all  
3 need a little time to sit back and think about it and generate some interest.

4 We only are a few of us here so I certainly don't want us to take up your  
5 time with things that aren't useful or central. My own view is that the recommendations  
6 that come here under I guess 14 and 15, which really are recommendations to States,  
7 again, I don't want to worry about whether the Common Rule should be amended or we  
8 should add a subpart to the Common Rule. We'll deal with that separately. Do any of  
9 you have any comments on 14 or 15, or then there's 16 and 17 which deal with  
10 professional advice, so to speak, to professional societies, and then 18 and 19 deal with  
11 advice or issues NIH might want to consider even though they're called  
12 recommendations. I want to come to 20 separately. But are there any issues you want to  
13 highlight for us as we think through these issues, at least those of you who are here now?  
14 They've received very little of our attention simply because we've been focusing on the  
15 more important ones, and I agree these aren't the same level of importance, but there still  
16 might be issues you want us to think about.

17 Bernie?

18 DR. LO: There was an issue this morning having to do with adequate  
19 funding to ensure these provisions. It seems to me that should be—

20 DR. SHAPIRO: We're going to deal with that.

21 DR. LO: That should go to NIH and to professional—

22 DR. SHAPIRO: Yes, those things we are going to deal with. We have to  
23 acknowledge that this cannot be done without resources. We're not the resource  
24 allocation committee for something but we have to acknowledge it and say we'd expect  
25 this, that it's unrealistic to do without supplying resources in some appropriate fashion.

26 DR. LO: I guess I would suggest that we try to be specific as to who the  
27 onus is on. It seems to me it's on funders, it's on institutions for IRB support if we're  
28 asking them to take on new tasks, as well as to professional organizations to articulate  
29 why this is all necessary.

30 DR. SHAPIRO: I agree. And I think there is some language somewhere  
31 in here that deals with that. But we need to bring it into closer proximity with these and  
32 other recommendations. These aren't the only ones, but other ones.

33 Yes, Bette?

1 MS. KRAMER: I was just going to say I think it should be a specific  
2 recommendation so it takes on more importance.

3 DR. SHAPIRO: We will. All right, we'll think about that and perhaps  
4 have something like that.

5 Recommendation 20 I just want to highlight for a moment because I think  
6 we ought to change it somewhat. It goes back to the issue of an appropriate agency to  
7 establish a mandatory IRB registry. At the current time, I'm not sure we've thought that  
8 through carefully enough or know what it is that we're registering to really require that. I  
9 feel quite uncomfortable with it as it stands. On the other hand, we will be coming out  
10 with a report on IRBs later on this year, at least not this calendar year but this academic  
11 year, if I could use that phrase, and I'd rather in Recommendation 20 indicate that we're  
12 going to have something to say about this issue as we deal with IRBs and something to  
13 say about the audit issue and how that ought to be handled rather than a specific  
14 recommendation which I think, for one reason or another, we haven't really worked out  
15 in our own minds.

16 So you will see that. We're not going to do anything without checking  
17 with the whole Commission. But you'll see something different come out on that  
18 particular one.

19 Bernie?

20 DR. LO: Can I make one other suggestion? A lot of this sort of research,  
21 particularly with drug studies, it seems to me is going to be done outside the purview of  
22 IRBs, well, outside the NIH but it may fall under FDA guidelines.

23 DR. SHAPIRO: That's right.

24 DR. LO: Should we say something somewhere that, even though for  
25 IRBs and investigators for whom this is not all mandated by regulation, we would advise  
26 they adopt it voluntarily as sort of good standards of practice?

27 DR. MESLIN: I think we already say that, but not explicitly. It's in the  
28 text.

29 DR. SHAPIRO: I think that is an important issue because as one thinks of  
30 regulations, guidelines, so on and so forth, it is much more complex given the way the  
31 research agenda is being distributed around different agencies and so on and private and  
32 public than ever has been the case before, which makes it both wonderful in a certain  
33 sense and more difficult in another sense. So we do need to acknowledge that, and we'll  
34 do so.

1 All right, my sense is that it would be a good time for us to adjourn unless  
2 someone has a burning issue they want to put before us.

3 Eric?

4 DR. MESLIN: It's not burning, I just wanted to know whether the  
5 Commission was interested in seeing a version of Alta Charo's recommendation  
6 regarding a call for more research on the willingness. Laurie has kindly offered to give  
7 some anecdotal data, but were you proposing that as a recommendation for us to work  
8 out and present back to the Commission?

9 PROF. CHARO: I was. There's a very first draft that still needs to be  
10 tinkered with. It can certainly be put out on e-mail for discussion. I'd like to see that.

11 DR. SHAPIRO: Why don't we put it up on e-mail and see. When you  
12 look at it, think of it not simply as a proposal but whether this is something we actually  
13 want to be part of our recommendations. We can get that up pretty quickly.

14 Thank you all very much. I appreciate it.

15 [Adjournment.]