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DR. SHAPIRO: Welcome. Let me call the meeting to order. Before we turn to the first major item of business, Diane represented us at a bioethics conference in Paris January the eighth, ninth, and tenth? I've forgotten what the date was, Diane. Eleven through fourteen. So I thought, if you don't mind we'll just take a few minutes now and hear what you have to say about that experience.

DR. SCOTT-JONES: Okay. The meeting that I attended was... actually there were two meetings. First the European Standing Conference of National Ethics Committees and immediately following that was the French National Consultants and Ethics Committee for Helping Life Sciences, and I'll tell you just a little bit about what happened at those two meetings. The European Standing Conference focused on the ethics of health care choices and there were eight paper presentations that explored this theme and I brought back copies of the papers—all of those that were available in English. And just to give you some of the highlights of the presentation, one speaker pointed out striking differences in health care spending among the European nations. They also talked about vulnerable groups such as the elderly and poor. They described citizens' juries, which were very interesting and which were used to gauge public opinion about health care. What they would do would be to constitute randomly selected groups of people. Those people would hear experts testify about various aspects of health care, and then this group of citizens would deliberate and make recommendations. They also talked a lot about the importance of education and prevention. After these paper presentations, all of the member nations frequently described their ethics committees and how these ethics committees had worked over the past few years. And it was an interesting variation among the nations represented. Some of the nations had ethics committees that had been long-standing. Others were just forming their ethics committees. And still others had not one national body but several committees that addressed specific topics related to bioethics. Also, during the European meeting, as most of you probably already know, there was a formal ceremony during which the member nations signed an addition to their previous document, which was their convention on human rights and biomedicine. Their addition prohibited human cloning, and I brought copies of those documents and also copies of the opening speeches that were made. Then, immediately following the meeting of the European group, the French committee had its annual meeting; topic of their annual meeting this year was racism in science. And none of those papers were available in English; only French, so I wasn't able to bring them back, but I did bring a program back from that meeting. This meeting was open to the public, it was very well attended, and it had been advertised with a poster that was an enlargement of this drawing on their program. The first part of this

meeting was opened by their Secretary of State for Health but it was disrupted by anti-abortion protesters. And also the first couple of presentations actually had to do with human tissues and human embryos, and those were also disrupted by protesters from the audience. Then, in the next part of the program they talked about human cloning. There were three papers on the scientific, the legal, and the ethical aspects of human cloning. And then also a presentation about the UNESCO 1997 declaration. And then after that the papers turned to the topic of racism in science. The topics included plasticity of the brain, the lack of scientific validity in the concept of race, and eugenics movements; this part of the meeting was closed by the French Minister of Education, Research, and Technology. He commented on the importance of speaking out on issues and in particular affirming principles that might go against the grain of public opinion. So that's about it. I have lots of detailed notes about specific presentations during this time, and I would recommend that we, in the future, if it's possible, have a member attend meetings of these groups. And I also think it's important that our staff continue to monitor developments related to bioethics in Europe and in other parts of the world as well and that we get relevant reports from these groups. The French committee didn't have specific papers at this meeting available, but they do have a document that includes all of their reports from their beginning, I think 1984 it was, through 1997, so we can order that volume, which would give us all of the reports that they've created during their existence.

DR. SHAPIRO: Thank you very much. We don't have a lot of time but if there are any questions for Diane now, we certainly, certainly should entertain them. If not, we can discuss those with you during the day as we have breaks and so on, but thank you very much for attending on our behalf and thank you for the materials and the focus you've brought our attention to. Alta?

MS. CHARO: One or two questions for Diane. I just want to make sure my memory's correct—that the cloning convention that they signed does not speak to the issue of making embryos for research purposes—it only speaks to, as they put it, making, or as we would have put it, making human beings?

DR. SCOTT-JONES: Cloning for reproduction.

MS. CHARO: Cloning for reproduction is how they phrase it?

DR. SCOTT-JONES: Well, I'm not sure that's their words; those are my words, but I have it right here and...

MS. CHARO: But you understood the intent to be only about making babies.

DR. SCOTT-JONES: That's what I understood.

MS. CHARO: Okay.

DR. SHAPIRO: Thank you. Any other questions? Going on? Okay, well thank you very much. I look forward to looking at some of these materials. Okay. The first large item on our agenda today has to do with the draft report that's before us regarding persons with questionable decision-making capacity or other titles we might use for this, and let met turn to Jim to introduce this discussion. As you all know, Jonathan, due to an unfortunate death in the family, is not able to be here today. Jim?

DR. CHILDRESS: Thank you Harold. Is this...? Can everyone hear okay? Let me just add to that we obviously will miss Jonathan very much today. We're very sad that the death of his father-in-law required him required him to go back after he'd already arrived yesterday, but he will be ready and eager to incorporate the kinds of revisions and changes we suggest today. I would propose that we reserve the most minor, verbal, stylistic, and editorial changes and send those to him and concentrate on the major ones, though of course, what is one person's minor problem is another person's major problem. Recognizing that, we'll proceed the best we can. Let me say a word about the schedule and what we hope to accomplish today in light of what we hope to do over the next few months. Before I do that, let me just offer a word of appreciation for West-Coasters. It's good for us to meet out here and see what you go through all the time when you come to the east coast. You have our deep appreciation for doing it so regularly. I guess the only consolation might be that since you do it so regularly, it's not as hard on you as it is on us. You guys are also younger. [Laughter] In terms of the schedule, a goal would be to have a draft in March that we could put on the Web for thirty days, on our Web site for comment from the public and from professional groups and others and then, after those comments have been received, and probably evaluated by staff and Commissioners, have another revision of that draft for approval at the subsequent meeting and then issue the report. Now, if that's the goal, and that's one that we've discussed with staff and Harold, it means then that we really are going to have do it today. That is to say we're really going to have today to reach some resolution on the major issues raised, particularly in chapters six and seven. The report has fared very well in the comments received from outside and inside on the first five chapters. Many praised the clear, balanced analysis. Problems arise in chapters six and seven, in part because we've never reached closure on directions, and as a result there are several inconsistencies there, several gaps. So those are important matters we need to talk about today and try to resolve. Before we turn to those, let me just offer a few other comments about this draft. First of all, you have Jonathan's note at the beginning, and this is Tab G, if I'm correct. Jonathan has comments on this current draft. Unfortunately those comments refer to the page numbers in his, not to this, so when you look for those

materials you won't be able to find them there. But, that aside, those questions are ones that we'll want to look at, though I'll propose that we focus first on risk and so forth and move through some of the others. A second comment on the draft is that the materials in bold include the changes for the last draft and for this one, so the bold materials will cover both of those. Some of the changes made for this particular draft obviously reflect very important suggestions that many of you offered. I don't know for sure that all of those have been adequately dealt with—you can tell much better than I. I would note that among recent ones that Larry McKay—I don't know whether he's yet with us—did send in a memo and Jonathan indicated he thought he'd addressed those proposals. We do have a more recent one from Laurie Flynn that obviously has not been addressed, and I hope we can attend to some of those issues today in our discussion. Also, this draft includes two sections of material from Paul Appelbaum that he prepared under contract for us. These sections are in the first chapter. One is the nature of disorders that affect decision-making ability. Page nine—at least if the table of contents says the right pagination—I haven't even looked at that. And then there's another section that does not appear on the table of contents. It's the penultimate section in chapter one and it's on the promise of research in this area. So that appears on page twenty-three in the draft, so you should note that. Both of those are new additions. Both are drawn from material that Paul Appelbaum's provided under contract for us. As a result of incorporation of materials like that there are some areas where transitions and connections will need to be improved. I would just note also, and this is not connected with any of Paul Appelbaum's materials, but that if you're looking at the table of contents on chapter six, there is a final section on the cost of special protections around page 140, and that does not appear on your table of contents. Now I suggested that the comments received, both from within and outside, focus mainly on chapters six and seven, and I want us to focus primarily on those materials ourselves. But before we do that, it seems to be to be appropriate to address first of all the issue of the title and thus the description of the population. We've gone around and around on this. And then second, just to see if there are any major problems in chapters one through five. Once we've done those two things we can then turn to the substantive issues raised in chapters six and seven and start with the analysis of risk and risk benefit and how we're going to deal with that. The title we have moved several times, from folks known as decisionally impaired persons to those with questionable decision-making, to most recently research involving persons with uncertain decision-making capacity, though that's not even reflected in the title that you have here; it's reflected in part of the draft but not all the draft. But I know at least one person has raised a question about whether even the current one is the best title for us, and again, it's not merely a matter of choosing a title, it's actually a matter of describing the population—the group we're looking at. And thus it is quite important for us to work out a category that will accomplish all that we hope to accomplish in referring to the population. It will be accurate but will not be offensive, et cetera, et cetera. Trish, I know you had a concern you wanted to raise.

MS. BACKLAR: I actually, can you hear me? ...actually thought that the title should be Research Involving Persons with Orders that Affect Decision-making Abilities, which is Paul Appelbaum's title for his little piece, and it seems to me that everybody fits in that and you're not being pejorative or unpleasant in any way about it.

DR. SHAPRIO: You want to repeat that title again just to make I...

MS. BACKLAR: Research Involving Persons with Disorders that Affect Decision-making Abilities.

DR. SHAPIRO: Eric? Why don't you go ahead. You're actually in a better position. Eric?

DR. CASSELL: I like that. I don't like the idea of persons with uncertain decision-making capacity because that's everybody. I don't mean that facetiously. I mean potentially anybody, if somebody wants to do studies, may not be able to make decisions. But you have no expectation that that's the case. They look like everybody else, and so forth. We're really about a whole population that we can characterize, and that has to be protected, rather than everybody who might one day, have uncertainty. So I really like that a lot.

MR. CAPRON: I must say Eric that I'm slightly surprised that you say that. I like it, but your past comments led me to think that you would say that everybody who has any disorder, physical disorder, not just mental disorder, suffers, their decision-making capacity suffers, and I think...

DR. CASSEL: It does, but we can address it in this. That's another, when we get to the issue of informed consent, and what that means, I think then it's possible to address it. Right now we have a concern for a population. We all know what the population we're talking about is, and we need to protect them. At the same time we're trying to make sure that they are able to participate in research and otherwise something is being lost to them as well as to the rest of us.

MR. CAPRON: I'm happy to see the title improve. I don't think that we have yet had resolution on knowing that we know what "the population" is. I believe we are still talking about two or three populations here, and there are going to be times, particularly in the later chapters, where there's, I think, some attempt to make statements that are perhaps too broad for all of those populations.

DR. SHAPIRO: Well, I'm trying to say a word about this. I think, one, I agree with what Alex has just said, and I think the title, it's fine, as are some other titles.

But this one is fine. I don't have any objection to it. The key is, inside the report, to describe what we're talking about with sufficient accuracy that we know what we're recommending. And that's really the key.

MS. BACKLAR: I do agree with Alex. And I was very concerned as I went through, again, seeing that this has become global, all these broad remarks, which there are different categories that may not fit in. And we do establish in the beginning certain categories. And that's a thread that is not followed through and needs to be.

DR. SHAPIRO: Arturo?

DR. BRITO: I think this is obviously the problem with, we're trying to categorize everybody into one neat category. And then, I like Trish's suggestion for the title, Trish. The Disorders that Affect Decision-making Ability. But then it doesn't quite include everybody because it's a very static thing, and a lot of these disorders are not so static. And there are potentially effects. So, the title's fine, but I think in the context of the body of the paper, if we use "isorders that affect or potentially affect," if it's described that way, because there are some disorders that can fluctuate and some that are respectively more, that a person loses the ability to make decisions....

DR. CHILDRESS: If there's a general consensus on this that we need, and I quite agree, to be more specific and accurate and precise along the way. And I hope that you in looking over this over the next few days, to get any additional comments in to staff and to Jonathan and me, will actually attend very carefully to that throughout the report.

DR. SCOTT-JONES: I just have one small suggestion based on what Arturo just said. Arturo pointed out that the deficits in decision-making may fluctuate and may not be there all the time. So I think if you took Trish's suggestion and just omitted the word "ability"—disorders that affect decision-making, then that might take care of the idea that it's not just an ability in the static sense that's affected, but that it's decision-making. So that would be my suggestion for changing it. Disorders that affect decision-making.

DR. CASSELL: Well, if they affect decision-making, and that's not an ability or a function, what is it?

DR. SCOTT-JONES; Ability meaning ability in terms of something that is there in a static sense. The ability to make decisions. It can affect decision-making at one instance rather than the capacity for decision-making in some stable sense.

DR. CASSELL: Diane, you lost me. I don't find that significant a difference.

DR. SCOTT JONES: Okay. You could have a disorder that affects your decision-making permanently so that you are never able to make a decision in the way that we would consider logical and rational. You could have a disorder that affects decision-making sometimes so that your ability isn't permanently impaired but that fluctuates.

DR. SHAPIRO: Alex?

MR. CAPRON: I don't think, Diane, that the terminology affects decision-making says anything about it being an even effect. I mean, schizophrenia is a disorder that affects decision-making ability by rendering that a fluctuating state. And the problem with the other stage is, cancer affects your decision-making ability. Cancer makes you be inclined to undergo radical surgery that you would not undergo if you didn't have it. So it affects the decisions that you make. We are talking about the ability to make decisions, and not saying that it is one thing or another with any one person. But it's affected by the very disorder that you're trying to do research on. That's the loop. That's the loop here.

DR. CHILDRESS: As I understand this, Alex. Stressing that capacity, ability, and even competence may not be global and permanent. That is, these are things that can fluctuate and that's actually the way the terms are used most consistently, at least in the bioethics literature.

MR. CAPRON: My only plea is that we use decision-making as one word. It's being used as an adjective here.

DR. CHILDRESS: Okay. Are we satisfied on that? Then let me see before we turn to the major issues that arise in six and seven, let me see if anyone has any major problems that you would like to direct our attention to in chapters one through five that we should get on the table. And then, obviously, depending on what we do with six and seven, we'll have to go back and make changes in one through five. Are there any big problem areas you want to note now, before we get into the last part of the draft?

DR. SHAPIRO: I'd just like—I'm trying to sit here and figure out what major and big means for purpose of making comments right now! But in the first chapter I've made a comment to the staff that there are a number of cases where there are assertions made for which there is either evidence or there isn't evidence, such as, "The

poor are over-represented amongst the mentally ill." I'm not questioning the statement, but if we're going to make statements like that we need to provide references for them. And so staff presumably can handle that without any difficulty.

DR. CHILDRESS: Paul Appelbaum has sent in another version of one section with additional references. But I agree with you that there are several sections here that could use, fuller documentation.

DR. SHAPIRO: I'm not going to bring up any other examples just as long as we make sure as we go to the next draft that for those that do have empirical assertions that we ought to reference it somehow so that someone could trace those down.

DR. CHILDRESS: Second, there is a sense in some of the material that's written in the area around pages 33–34 if I remember correctly which say things about commercial gain as if that's a bad thing. Now maybe it's a good thing, maybe it's a bad thing, but it's not, on the face of it, one or the other. That is, if the system works, commercial gains is supposed to be available when you're doing something people want. And otherwise, you don't make commercial gains. Now I don't want to go into a long discussion of economic markets and so on and so forth, but I am a little sensitive to the issue of whether we, just in noticing that there are profits involved or gains involved, that's necessarily undermining something important. And I just think we have to be careful with the language. Eric?

DR. CASSELL: There's an implication that in the 1950s when thyroxine was introduced that the same standards of protection of human subjects were present as are present now and that they were somehow abrogated. And it wasn't bad at all. I mean, I know very well from personal experience that people used research subjects without consent because we all had their best interests at heart and they didn't need to consent. And that was a common thing at the time. So the implication that bad people were doing bad things because they wanted to rush to market is just not there in that context.

DR. SHAPIRO: Thank you. Alta?

MS. CHARO: On the other hand, Eric, without disputing the accuracy of your memory, in the context of the Human Radiation Committee's work, Alan Buchanan was asked to do a historical review of the standards in place among professionals at the various times when these radiation experiments were taking place. And, as I recall, he had documented that there were a variety of formally adopted professional statements that required things like notice on consent that should have been used by professionals at

that time. So I don't think we want to be overly sympathetic either, since there is evidence in the human radiation record that professionals failed to implement their own statements of professional obligation at that time, even though that failure was so widespread you might say it was a standard practice.

DR. SHAPIRO: Well where does that leave us?

MS. CHARO: I think it leaves us simply with two comments on the record to make sure that the staff has both of those points in the transcript as they continue to work on the revisions.

DR. SHAPIRO: Alex?

MR. CAPRON: As we were reminded by doctor McCarthy in his paper for us, at the time that the NIH developed its first rules for research with human subjects, those rules were being applied to normal volunteers. But the same processes were not being applied to patients for the reasons that Eric describes, and this is in the 1950s and '60s in the federal government. So I think, for better or worse, there was a widespread sense that the rules that came out, particularly the Nuremberg, were really addressed at using people who were not sick, and using them solely as guinea pigs. And of course, the declaration of Helsinki also made that divide between research with volunteers and research on the diseases of the patients you're researching. So, for better or worse...I mean, I think Eric's description of his memory of probably what he did as a resident or whatever, in terms of how he was told he should get consent or not get consent depending on whether he was working on a patient with the disease that he was studying reflected common practice, even at the NIH, into the sixties.

DR. SHAPIRO: Well these are very helpful comments. Any other comments on major issues you would like to see addressed in chapters one through five? Any other concerns? Jim, are there any issues in those chapters which you would like some response to?

DR. CHILDRESS: No. There's really been, as I mentioned, a very favorable response to those chapters from internal and external reviewers, and though there are problems of the consistency, inconsistency at different points, some of those are editorial things that will need to be addressed. But on the whole I think those are in fairly good shape. Eric does have one he would like to raise, though. I'm sorry, this Eric here. Okay.

DR. MESLIN: Just very quickly in chapter four in the discussion about risk assessment that begins on or about 75 and runs for three or so pages—we'll be

discussing risk in more detail in a few minutes. But I did want to bring to the Commission's attention that I had a conversation with Jonathan on the plane coming out about the way in which he discusses risk assessment rather narrowly in those pages. It doesn't allow for the way in which subjective assessment s of risk by both experts involved in risk analysis and by patients or subjects who have their own values about what risk means, could be incorporated into that. And Jonathan was sensitive to that and I suspect it'll come up in our discussion. But I just wanted to flag that because he recognized that it was a rather limited presentation and that more could be done over those pages.

DR. SHAPIRO: Thank you. Eric?

DR. CASSELL: I'm sorry about this little nit-picking thing, but it's a style matter that has to do with what all the things we write. I presume that we are trying to write nonsexist language in these documents and that's my own attempt. And on page 132 there's a discussion of what the potential subject must understand and that's entirely couched to the potential subject that's a she, and since it's not a subject of ovarian research I think it's inappropriate. I think nonsexist language is what we ought to have and that means either gender designation. Potential subjects "they" would do the same thing as the potential subject "he," "she" or whatever.

DR. SHAPIRO: Thank you. Other comments, particularly on the first five chapters, because Jim wants to begin somewhat differently as we go to chapters six and seven. Trish did you have a question you wanted to raise?

MS. BACKLAR: No I decided not to, actually.

DR. SHAPIRO: Okay, thank you. Not like yesterday when we forgot it! Today we're just not mentioning it.

DR. CHILDRESS: Well let's turn to the issues in chapters six and seven, and let me just note one thing at the outset. It was actually a very sobering discussion yesterday to talk about the problems that arise if we want to change the common rule and so forth. Keep in mind as we look at six and seven we are talking about some recommendations for changing regulation. We're talking about some recommendations directed at investigators and IRBs. We're talking about some that can be implemented by state legislature and so forth. So there are different levels of recommendation. So as we are thinking about the recommendations we want to make, I guess it may be helpful to keep in mind our discussion yesterday, for better or for worse. I also would just note an observation that came to mind after our discussion or in the context of our discussion yesterday of the tissue samples and the helpful points made by several, including David

Cox. And in many ways one could take David's comments and just substitute in the words "research with persons with disorders that affect decision-making ability" and make the same point. What we're interested in doing is developing guidance in an area where many have felt more guidance is needed to facilitate valuable research and to protect a patient subject's rights and interest. And it's that kind of balance, it seems to me, that we're trying to seek in the recommendations that have evolved so far and that I'm sure will undergo radical surgery today. Let's start with what I think is the main one, one that relates to a comment that Eric Meslin just made, and that is the question of risk. That obviously is important throughout the report. It's important in the way we characterize what we want to recommend in chapters six and seven, the kinds of protections we want to offer. And several issues arise—not only the adequacy or completeness of the way risk is understood here, but also whether having two categories of minimal risk and more than minimal risk or greater than minimal risk, whether it is sufficient to have two of those. Or whether we need to have, as Laurie Flynn has suggested and others have also commented, the category that is used in some other areas and that is for slightly more than minimal risk, or minor increment over minimal risk. Whether we need that category—an intermediate one between minimal risk and greater than minimal risk. We have the discussion of what counts, apart from the addition of another category—we had the discussion last time, and a very helpful one—about what would count as minimal risk, can we say more about that? And we did get some materials following the last meeting, materials from the FDA from Ronald Wilson, who was at the last meeting. And those appear in Tab H. I won't go through those now but I just direct your attention to those and Eric Meslin may well want to comment on those because basically it was a response that in FDA there's been greater attempt to think more about what would be involved in minimal risk and to give fuller examples and to use the line. It's G, the G Tab. So that's there. What I would propose we do is open this up for discussion on this very central category that plays such an important role in the way we deal with our recommendations. When we see the chart on 154, for instance, our additional consent requirements really hinge on whether in the first instance there's subject risk, whether that's minimal or greater than minimal. And most of the recommendations here have to do with greater than minimal risk. Sometimes we say that all of them do but that's actually not true. And there is an inconsistency in six and seven on this particular point. There are some that we do extend and we'll come to some of those later, and talk about other protections once we get past the central discussion of risk. For instance, no apparent dissent is one that actually we say on 124–125 which applies to all the categories, so there's some problems of inconsistency. However, this dividing line between minimal and greater than minimal certainly is central to what we're about. And then of course the other dividing line that we'll have to move toward in our discussion is between therapeutic and nontherapeutic or that are put here in terms of whether there's a potential direct medical benefit to the subject or not. So we're starting in with risk and obviously we'll have to move to benefit and its relation to risk. So I

propose, Mr. Chair, that we open the door to this discussion of risk and see what people think about what is presented in this draft. How we need to modify it, if at all.

DR. SHAPIRO: Thank you very much. Questions, comments from members on this issue? I think everybody got a copy. Did everyone get a copy of Laurie's e-mail? I think she sent it to the whole list. Alta?

MS. CHARO: I'm perfectly happy to get it started. Jonathan has repeatedly peppered people from the Human Subjects Committee with a note with me and Trish in particular with requests that we actually address this, and I found that in the end I couldn't address the merits of whether or not there ought to be a hierarchy of three categories of risk versus two as an abstract question. I kept coming back to how I thought the categories should be used. Putting aside the administrative difficulty of interpreting the meaning of three categories since we've had such trouble interpreting two. Right. But putting that aside as a practical problem I've found that what I kept worrying about was which kind of presumption I wanted to operate under. Was I trying to get as many people enrolled in research as possible, or was I trying to keep as many people out as possible? If I was trying to keep as many people out as possible I wanted to keep it to two categories where the largest possible number of things was going to be defined as greater than minimal risk for which the extra protections would be in place, some of which might result in people not being eligible to be enrolled. And it was all consistent with a mindset that said that the primary concern here is abuse of people who are unable to protect themselves and are being volunteered inappropriately by others, versus a kind of mindset of wanting people enrolled because it is very important to move this area of research forward and occasionally is of value to them. And every time I began slipping into that second mindset of access being the primary concern, I found myself remembering that the whole origin of protection of human subjects is premised on the idea that sometimes certain research just can't be done. If you go back to the National Commission Report, they recognize that very explicitly. That that is, in fact, the tradeoff that we recognize, that that is a tradeoff that we have accepted as being desirable because of what you gain by never abusing somebody in a way that's really quite terrifying when you begin to think about it in a really kind of personal way, imagining what it would feel like to wind up being used in a confused state without wanting to be there and being unable to protect yourself. And allowing myself to step into those shoes, finally, I think, although I'm still open to persuasion, I think finally, comfortably put me in the cap of still wanting to be overprotective instead of underprotective if I'm going to make a mistake. And that in turn led back to the desire to keep the categories at minimal versus greater than minimal, keep them simple, keep the extra protections operating across the widest possible range of interventions.

DR. SHAPIRO: Thank you. Other comments. Trish?

MS. BACKLAR: I actually agree with you Alta, and I'd like to say why I agree, because I think it may make it clearer to the, if we're going to have this discussion. If we take the premise that we're looking at when we discuss minimal risk, the minimal risk of the population being studied, that is going to, I'm taking that as what we're going to do because in the beginning I was not sure that I would agree with that, but now I am. So if we take a population of people who have, for example, schizophrenia, we know very well that their everyday risk is really quite high, even though it's a heterogeneous population and there are some people who will have less risk and some people who will have more. We know that we're dealing with people whose everyday risk is vastly different from a healthy person. And that enables you to peg exactly what just it would be to be in a research protocol where nothing much more was going on. So that almost anything that you do with this population that alters that everyday situation is greater than minimal risk. And you begin to have a little picture in your mind, instead of it being so abstract, of what it might be for somebody in this population to be in a research protocol.

DR. SHAPIRO: Thank you. Bernie?

DR. LO: I think the question of how many categories of risk we are going to have can't be separated from the question of how we're going characterize benefits and what kind of protection. So it seems to me on an intuitive sense, risk benefit and the type of protection are related. And my only concern is that there's a whole spectrum that we're trying to put into categories. And it seems to me that the danger of collapsing is that you may not want the full panoply of additional protections for all types of research that involve more than minimal risk, particularly when you factor in prospects of benefits. So I think we get back to this in other ways, but ultimately it seems to me we've got this three-by-three matrix of risks, benefits, and protection, and my only concern is that we recognize that the final sort of muddle, that there may be some protection we want for some types of studies that are more than minimal risks and additional ones in other types of studies.

MS. CHARO: I agree with you Bernie, and it does make it harder to discuss this. But let me give you a concrete example of what that might look like based on what Jonathan's written and what we've been talking about. Well, because you were on the Genetics Subcommittee, right? Greater than minimal risk research might be that kind of research which cannot be done in the absence of justifiable benefits, so, for example, it might be the premise of a rule as suggested here that you simply cannot do it unless there is direct benefit to the patient. But even assuming there is, and it is possible to be enrolled in greater than minimal research with either giving consent yourself or with consent from a family member, we might nonetheless find that there are special protections that are triggered not by risk levels but by things like settings. If you are in

an institutionalized setting, if you PI is also your treating physician. These might be context that trigger additional protections not tied to the risk benefit ratio or to the level of risk in an absolute sense, but they're special contextual circumstances. So we can have separation among these things.

DR. LO: Right. But it seems to me that studies that are more than minimal risk but of not direct benefit to that individual patient may still be poor in terms of basic knowledge about the condition the patient has, which may lead to future therapeutic intervention. I'm not sure that possibility is captured in a matrix just with say, minimal or greater and direct benefit or not direct benefit. And I may be willing to have a little more than minimal risk when there is not direct benefit but really profound understanding of the same condition the subject has that may provide therapeutic, you know, I'm not just blowing smoke. I just think you have to draw lines. What I don't want to do is close off research that leads to a basic understanding of the disease process, without which it's very unlikely we will get therapies for these conditions, you know, really effective therapies.

DR. CHILDRESS: Let me just note for the record if I could, Harold, that the kind of argument that Bernie's making is very close to the one that Laurie's made in her statement, and I think the reason for mentioning it now is we want to put it by record of where we've discussed these issues. And I take it that the kind of position you're recommending is one that will be similar to hers as well, in which you're basically trying to increase attention to the significance of what is often called nontherapeutic research and not directly beneficial in relation to risk. But that's perhaps going to force you to add that third category: the slightly more than minimal. So I think you're right in the intuition that even though we start with risk we have to move to the other. The question is now how we're going to put all the pieces together even though we've started with the risk part.

DR. LO: If I could Jim, just to take a little more time, I mean the examples I have in mind have to do with doing a imaging study like an MRI scan or even a PET scan on someone schizophrenic. Now from what I've learned, that can be disturbing to someone even though they may have a similar test in a clinical setting. And if the study really is going to be a crucial study in understanding the locus of where abnormalities take place so that new therapies can be targeted, I'm just trying to get a handle on how they deal with that. Because it seems to me that there is probably more than minimal risk, but to go back to the old language, that's slightly more as opposed the whole, whole lot.

DR. SHAPIRO: Okay, there are quite a few people who want to talk. Trish and Alex, Diane, and Eric.

MS. BACKLAR: I think we have to distinguish. We're muddling things together. One is that if we're talking, and I have to go back to the schizophrenia model because I know it the best. So we're talking about protections for a particular group of people, and we're muddling up now benefits and risks and how much the risk is. First of all, the reason we are suggesting protections for this particular group of people is because, if they have a psychotic period, which they could have, which may happen whether they're on medication or off medication or if they're having an MRI or whatever it is, you'd want to have those protections in place if they're in a research protocol. So that's just because of the nature of their disorder. The other aspect of this is, it seems to me, and I think that the e-mail exchange between Larry and Alex was extremely important in looking at when we start to try and balance benefits and risks, I think I agree with Larry. The risks are risks, and one needs to look and identify what those risks are, and it's risks of harm. The potential benefit is something that one might look at, but not in the same way. It's the risks that you must identify. And part of those risks lie within the disease process itself.

DR. SHAPIRO: Alex?

MR. CAPRON: I find myself feeling that our desire to simplify the subject has taken a terrain that is so complex and flattened it a lot. It seems to me that the kinds of processes that we think a good IRB should go through, would indeed take into account what Bernie talks about. I don't personally have confidence that every IRB, even supplemented by two members of the patient crew, are going to be able to assess really well, however, the question of how fundamental this research is. And there's actually a sort of a two-edged sword there, because the very assertion that research is very fundamental and very important could lead, and can lead people to think, not quite "anything goes," but the justification for potentially harming someone is greater. Then we have the question of the different diseases we're talking about. It seems to me enormously different if we're talking about a person with Alzheimer's disease who has made some indication of their willingness to be in research, versus a young child with a mental disorder whose parents are making the decision. And then the context of whether this is a child or a person who has been institutionalized for whom the caregivers may be very involved or they may be, the responsible surrogates may be very involved or they may be very uninvolved and very subject to manipulation by the researchers. It's very hard, it seems to me, to generalize across all these different categories. And I don't think that the matrix that we've developed yet does that, and I don't know how to get out of it other than saying "Well, these are the rules for adult schizophrenics living with their families, and these are the rules for adult schizophrenics out in the community, and these are the rules for people who get picked up off the street and taken into a mental hospital and are confused." The context means so much. I'm with Alta in the sense that right now, in light of what we've seen, I want to be protected, because we've seen so many

contexts in which institutionalized patients in particular have been abused. But I also very much understand Laurie as someone who speaks for the families of people with mental disorders and says, "You will create incredible frustration and indeed we will fight this tooth and nail," which is, I think, is the subtext and we know what happened to the recommendations in 1978. If you don't allow some mechanism where people who are very knowledgeable about this disease, who live with children with this disease, who really believe they are doing the best thing to allow the child to participate so that some basic finding can be made about something about the way the brain works or whatever. And if you were in that situation it would drive you crazy to think that someone had said that there's no way you're really going to be able to really get consent in that situation. Because it involves a more than minimal risk, meaning that it involves a lumbar puncture, and getting some spinal fluid. But I just don't know how to deal with this, frankly. It's something that is going to go a few pages at the end of this and can be stated in eight pages of federal regulation. I'm sorry, and I know we've been enjoined by Larry and others to keep it simple, make it simple, you know, help the overregulators, you know, but this subject just does not boil down that simply. Everything is in the details here.

DR. SHAPIRO: Thank you. I'm...

MR. CAPRON; I guess my bottom line is I'm willing to go with more restrictions for the moment, as Alta is, because of the experience of the abuse, but I know we're doing a wrong to some people to do that.

DR. CHILDRESS: That's that balance we were talking about earlier, and we may try to resolve it differently. The question is, it seems to me that, to take a radical approach here, Alex, is to say, "Well, we shouldn't, we should just provide a kind of analysis and indicate the problems and not come up with a recommendation." I think you don't want to go that far.

MR. CAPRON: No, but what I wonder is whether we have to press on this, and I don't think there's any harm in putting out a draft that doesn't do that but that recognizes a question for the people who are going to read the draft is do we have to break this down into categories, and do we have to address separate, I mean my major concern is between the institutionalized and the noninstitutionalized, frankly. Because I just think total institutions are places where abuses are more likely to occur because everybody there is subject to a different mindset than they are where there are, I don't have to explain it. You understand.

DR. SHAPIRO: Okay. Diane? Then Eric after this.

DR. SCOTT-JONES: I see what Bernie's saying, what others have said

about the importance of not restricting research that might in the future provide important information for whatever disease or disorder is under consideration. But I suppose in thinking about it, I just don't see how one can make that kind of decision if you're trying to balance risk against expected or potential benefits, you just can't do that as simply or even with a lot of thought. And I worry that in the way that we present this, we may just ever-so-gently tilt our discussion toward the side of research going forward and not being more balanced, or, being in favor of the protection of people who are in the studies. And I look at how we express the notion of risk and benefit. And even though all of us realize that benefits are only expected benefits or potential benefits, the same way risk refers to expected or potential harm, still, in our language, we slide back to talking about benefits and risks, and we really should not do that, because the benefit cannot be foreseen. You cannot say, going into a study, that the results of it will be beneficial, that's a promise, and I think we have to always acknowledge that you can't know that before the study is done. You're going on faith that the research enterprise in general is going to lead to good. And for a given study, it just isn't a judgement that you can make. And I would strongly urge us throughout the whole discussion of this always to use the word "potential benefit" or "expected benefit" so that we remind ourselves and any reader that it is that. It isn't a certainty that a benefit is going to occur, the same way the word "risk" in and of itself conveys that it isn't a certainty that a harm is going to occur.

DR. SHAPIRO: Thank you. Eric.

DR. CASSELL: Well, I have just as much of a problem as everybody else does. But taking from Bernie and Alex, it actually isn't risk that we protect people against, it's investigators who expose them to risk. They do so in the pursuit of their research, and we permit certain things to be done if the potential benefits and so forth occur. On the other hand, that what I am doing is seminal work and will lead to ... I don't want to have anybody doing anything who doesn't have that kind of faith. And who isn't working with that intensely. So we have to protect people knowing that every investigator believes that what they're doing has some value or will lead to something good or they shouldn't be doing it. So that's the first thing. That doesn't move me, that it's going to have benefit, and therefore we can be lax about risk. The second thing is, I'm always worried about classifications that get too simple because we're in an unsimple situation because they misclassify. You can't do otherwise. You just can't have a bipartite classification in a complex area and not go wrong in one way or another in individual cases. And so I come down finally to believing that in fact we do require three categories at least, minimal, somewhat or whatever we're calling it, over minimal risk, and risk. Because a lumbar puncture isn't everyday risk, but on the other hand it isn't very great and it may be, in fact, necessary to this particular study to get spinal fluid. And I would hate to see the lumbar puncture be part of minimal risk. It isn't part of minimal

risk. So I come down for the three, ultimately for the three, I don't think you can duck it. That's the other thing, I don't think you can duck the issue. Because to duck the issue is not really to duck it at all but to make it something where it is now, and we're having problems with now, so I think we're forced to come to something. And I myself like Laurie's division of it.

DR. SHAPIRO: Thank you. Tom?

DR. MURRAY: I'm also sort of picking up on Laurie's concerns, particularly about families. And I'm wondering if it would be possible for our recommendations to sensitively reflect that families are different. A family that decides, which feels that a slightly more than minimal risk, or minor increment over minimal risk procedure like a lumbar puncture, even though it's not intended, not directly benefiting their child, might, that, it seems to me a decision families ought to be able to make. And I'm not so clear that I would give it to the, you know, someone who didn't have the same sort of lifelong, intimate connection with the individual; in an institution, in Alex's case. And I think we may want to further subdivide among institutionalized and noninstitutionalized. I'm not sure, but I do think that we want, if we can, we want to acknowledge that families may, that families are different. And not all families are good families, and we don't want to be Pollyannish about it, but many are and I think we do want to try to acknowledge that if we can. I suspect we can.

DR. SHAPIRO: Thank you. David?

DR. COX: I think Eric and I were born under the same sign, I just, he stated a lot of what I wanted to say, but I'd like to emphasize two points.

DR. CASSELL: That's because they heard it from you yesterday.

DR. COX: So it's this idea of really aggressive researchers, again. I think you want aggressive researchers because they believe in what they're doing. And you don't want to set a bar so high so that they can't do it, their research. But if it's questionable, you want, the more questionable the research gets in terms of its benefit or the risk to people, you want the bar to go higher and higher and higher. And as a researcher I would be very uncomfortable, I have been very uncomfortable when the bar isn't high. Because I will go and I will always take the lowest bar I can have, because it allows me to get my research done. So I think I would be very against setting things that would make research impossible. But I really like the idea of tiered bars that, when it gets more and more questionable that it gets harder and harder to do. And that's why I'm in favor of the three things also. I really am extremely uncomfortable with the idea of making the world into these two sets of things; like I said yesterday, apples and oranges,

and then you get this yellow thing and you say what is it? It's not round and it's long and it's yellow and it must be an orange, I guess, because it's not an apple. And that just isn't practical. You can't have a million different classifications, but I think that the lumbar puncture was a good example. So the, I really like the idea of having the researchers have to go through harder and harder hurdles, but to give them more than just it's really risky or it's not risky at all.

DR. SHAPIRO: Thank you. Bernie?

DR. LO: I think this is a very useful discussion. I think this kind of complexity needs to be part of the report and public debate. I tend to have a very literal mind. I work much better with cases rather than abstractions. I'm just wondering if we could set forth a couple of examples of minimal risk and not minimal risk and therapeutic benefit and indirect benefit and then see how our matrix on the last page plays out. Because I think the bottom line is that we want to make sure at the end of the day when someone comes up with a protocol and we go through the guidelines and content. It's all just like we have to do this or can allow them to do that. That makes sense in the context of the study, factoring in all the other things that have been raised. Whether the subjects are going to be institutionalized, the extent of the family involvement, what kind of family, and things like that. And I guess, without having a clear idea of how this actually works out in situations we're likely to come across, it's hard to have an abstract discussion, so again, just a plea to work up some cases and see how it works out.

DR. CHILDRESS: These are not cases, but on 149 and 150 we have examples offered of minimal risk and greater than minimal risk ....

DR. LO: Right, but I think ultimately the classification of risk is useful, because we're going to take that analysis, put it into an analysis that has to do with type of benefit, other factors, and then make recommendations as to what protections are required. Which, I'd like to see the whole thing come together in tableau.

DR. SHAPIRO: All right. Thank you. Trish? And Arturo, you're on the list.

MS. BACKLAR: I have this in three parts at this point. I wanted to respond to what Tom said about families. In the best of all possible worlds, families usually try to do the best they can for the person that they are involved with who may be ill. But as we saw with the people who came to talk to us about their relatives who had been in research protocols, they may have such a difficult time in just accessing treatment that they will be very eager to put their relative into a research protocol, having that therapeutic misconception that they're going to get care where they didn't get care

before. And so, in a sense, when Alex talks about the institutionalized people and people who aren't institutionalized, in talking again about people with schizophrenia, we have some of the same kinds of things that may obtain whether one actually is in an institution or whether one is in the community. And this is why it is so complex and why we're having such a difficult time with this. Because we have to factor in all of these issues, which is why I keep saying you've got to factor in all those other protections.

MR. CAPRON: Take Eric's case.

MS. BACKLAR: What case?

MR. CAPRON: Take Eric's case of a lumbar puncture. Should the family be permitted to give permission for that, even if it's a nontherapeutic protocol.

MS. BACKLAR: Well, it depends again on, to go back to Bernie, on the whole context. The issue that I find so difficult here is that all of this is context dependent. And we are talking about it in the abstract. And I don't know who's going to be making the decisions. There's a lot here that we can't pin down. Which is why I keep suggesting with this particular population, yes, I would have the families involved. Absolutely. But I also would have a private practitioner, who is like a monitor for the study. Because you need checks and balances. The family may be so eager, somebody has to say, for this particular person a lumbar puncture would be a dreadful thing to occur. And it may cause them to become very ill, great discomfort, all of these kinds of things. And I'm not at all certain what we mean by nontherapeutic or therapeutic research. I find this exceedingly confusing, based very much, and I agree with what Diane had said, that all research is, in a sense, hypothetical. It's very well described in the *Belmont Report*, the outcome is very unsure.

DR. CHILDRESS: But the difference here would be whether there is no potential direct medical benefit to the person versus potential medical benefit.

MS. BACKLAR: But is still is potential.

DR. CHILDRESS: That's been taken, the point's been well taken...

MS. BACKLAR: And somebody's going to have to make decisions about this and then we have the problems with the IRBs. So I want to say that I think we have a big responsibility to set up adequate protections for these subjects.

DR. CHILDRESS: In this discussion keep in mind that even though we're dealing with risk benefit of doubt, trying to figure out what we want to say there,

the rest of the discussion we'll have this morning will focus on a whole set of other protections. Many recommended here, and others you may want to recommend. So, they're here, but, it seemed useful to start with what has been the most controversial point, namely how we're to work out the categories for risk and benefit.

DR. SHAPIRO: Okay, I have quite a few conventions I want to speak to, I wasn't sure whether you had...Steve?

MR. HOLTZMAN: Alta suggested that we just start on the analyses by asking are you looking to enable research or are you looking to potentially to erect the greatest barriers to harm, and that that should be logically primary. I guess I start in a little different place that's not inconsistent, and it has maybe tie into Tom, is that, where do you locate the locus of judgment? I mean, when you have to look at things where you can't make decisions other than by getting into the richness of the context, that means judgment is involved. And then the question is, who has the locus of judgment and what are the conditions under which one would say that the State will impose a certain barrier to private individuals making, being the locus of judgment. And why I'm inclined to a richer scheme of three is that, it seems to me, three categories of risk is that I can see where the State can come in and say where there is significant risk, all right? That the locus of judgment can't—we're going to erect a protection—even for those who would claim to speak for that individual in the absence of the individual being able to speak to themselves, that this can't be done. But when I look at the greater than minimal risk but not, whatever, I don't know the exact terms, I then think about how we do locate the locus of judgment there in things, in people other than the State, who are qualified to speak for another.

DR. SHAPIRO: Thank you. Arturo?

DR. BRITO: It seems to me, taking the last couple of meetings and this one, that we have spent a lot of time discussing this issue of minimal risk what is and what isn't, and I have yet to hear a good way to define it. I want to touch on something that Eric said and then kind of continue what Trish is saying about the context of the situation or the investigation. What I've heard from public testimony and the readings has been mostly complaints, not so much from the public about "Oh, I didn't know it was going to be such risky research," or "I didn't know that I was putting myself in this situation"—it's more of a context of "I was deceived. They didn't take the time to explain what the research was," et cetera. So it seems that, I'm not sure if it should be two, three, a hundred categories, I'm not sure that's really going to make a difference. Because when it comes down to it, it's the investigator's responsibility to make sure that the individual on the other side understands in their language, at their educational level, what is going on. And if that person is not capable of doing that, it seems that the

investigator is responsible, or the IRB or whatever body is responsible for overseeing the research, is responsible for making sure that there is a representative that is independent of that research. So maybe the emphasis should be that the higher that bar is raised, to use David's words, that therefore we need to emphasize more the needs of the independent person to represent a person who has decision-making inability or lack of ability, or questionable ability, whatever term we want to use. And not worry so much about what category. Because it seems like the category hasn't been the issue. Of course when there's obvious severe risk, that's a different issue. But when we're talking about gray zones here, and something can be minimal risk in one situation or greater than minimal risk in another situation, it just, I'm not sure why we're spending so much time on this issue. Not that it's not important, but I don't see how we can come to any conclusion with this. I think the emphasis should be more on the deceitfulness that can occur and is not explained, and then allow the person or the appropriate representative for that person to make the decision for themselves whether or not they think the risks outweigh the benefits or the benefits outweigh the risks.

DR. SHAPIRO: Okay. Alta?

MS. CHARO: One of the reasons why the question of deceit, I think, becomes so emotional, is because it goes directly to why it is that we ordinarily don't contemplate research that hasn't been agreed to by the human subject, and that is the idea that you should be in control of your situation. I remember being quite affected by lectures on military history which talked about how a lack of control over circumstances was the way that people actually are driven crazy. And I want to remind everybody here that the very prospect of enrolling people without their ability to consent in even minimal risk research represents an enrollment that violates the usual rules that people don't enroll without volunteering on their own. So even having people entered into nontherapeutic minimal risk research represents a deviation from the ideal. Then we talk about a minor increment over minimal risk, and I hear Bernie say this and about the losses and I hear Alex and others talk about the frustration of certain families who want very much to be able to further this area of research, perhaps in the hope that in their own lifetimes there will be some benefit from that research endeavor, or perhaps just out of frustration in general with the nature of the illness. And I'm very sympathetic. The strength of diversity on commissions is that we all have a lot of different personal experiences, and, like several of you, I'm sure, I've been involved in these situations. To me this doesn't argue for more categories, necessarily, which may just multiply the problems of definition. It may argue for keeping a simple or perhaps even just the binary distinction, but building in an escape hatch that is entirely individualized to all the questions of context, such as institutionalized, noninstitutionalized, a family that's there four times a month versus a family that's there four times a year, and really experiences with this person their own illness and reaction to the research, et cetera. So one could

imagine, for example, anything above minimal risk, would have a (that is nontherapeutic) would have a strong presumption against it. But that there is an ability to bump this to an extremely independent group of people who are not driven by the investigator's own determination to get the research done, but is, in the model of the hospital ethics committee, when it worked properly, something that takes everything totally (and some people are smiling—it depends on your experience on the hospital ethics committee). But takes everything very much in a particularized manner. But starting with the presumption that you can't enroll them. I mean it sets an extremely high but not totally impassable barrier that might offer an ability to particularize these situations for the few people, as Alex put it, that would be wronged by being told they absolutely cannot be enrolled, and at the same time I find still that the locus of control, Steve, should be, in fact, that some people can't make some decisions. We simply will not allow people to be enrolled. Because we're already doing enough, we're already drafting these people who can't consent into medical research when it's minimal risk, and I think that's about as far as you want to go on a regular basis.

DR. SHAPIRO: Jim?

DR. CHILDRESS: I know there's some others who want to cut in on this topic, so let me just propose that we think about the following. Finish up our discussion, the several other comments that remain on risk in relation to benefit. And then sort of put that on hold and talk about the other protections that are present here that are being proposed. And then, at the end, come back and ask in the light of those other protections, do we think, and we need to get, again, some sense of direction here, do we think that we can go with the categories that are present here and the protections that are then being triggered, or do we think we need to modify in the direction, say, of three levels of risk. Because, if we're going to have a report, we need to move along some of those lines. If that makes sense to people than maybe, Harold, we can finish up the comments on the risk and relation to benefit and then move to the other protections.

DR. SHAPIRO: All right. I do still have Eric and Trish who wanted to speak, so let me turn to them, and then see, Jim, if you have any further comments on this, and then we'll move on and come back to this as appropriate later. Eric?

DR. CASSELL: Well I think we have to see what we're doing on this particular report as one of the reports that will come from this Commission, and that what we are doing now will be amplified and further discussed in the other reports to help solve the problems that we raise. The change in what happened in the 1950s was, people with physical illness, and we'll leave out psychiatric disease for the moment, so that we weren't doing research on people without their consent, was not merely that along came regulations and now everybody knew they had to do it because doctors have

been evading regulations since the beginning of time. And it wasn't, it was also a change in the perception of subjects, which was partly what happened in an entire culture as sick people became persons and were seen differently. And then, there was the increase in knowledge of investigators about the whole subject about the rights of patients about what their obligations were. So that the research climate in the 1980 and 1990s is a totally different climate, not merely because of regulation, but because of these other changes. What we have heard about the subjects of psychiatric research suggest that they are still being seen as nonpersons in the research that we heard about. More, maybe not as badly as years ago, but more so than we know about people with physical illness. We try to put regulations in place because we want a kind of research to go forward. That's actually why we're doing this. Otherwise, we'd just leave it the way it was and there would be no further research! In any case it wouldn't move in the way that people want it to move at this time. We put regulations in place to protect our subjects in the event of moving forward, and we would like there also to be a change in the perceptions of those subjects from the way they were seen before. One of the things that has helped do that is the family, and the surrogate decision-making, because that makes that subject a person—when the investigator has to talk to that family or that surrogate, certainly to a greater degree. Ultimately, I think we should have three levels: I think we should see ourselves, knowing we're going to move, when we discuss the IRB, in how does the IRB solve this problem? Here's how we think the regulations should go, now we're going to see how do we think the IRB should solve the problem beyond merely implementing regulations. And then ultimately when we get to consent and so forth we're going to see how, in fact, do we educate our investigators about this so that they are brought to it differently. So I think when we look at this, from my point of view we should have three categories, we should know we're trying to move things forward, but we should also know that we have other ways to go at this, attacking other sides of the problem as our work goes forward.

DR. SHAPIRO: Thank you. Trish?

MS. BACKLAR: I want to say that I, the issue of the categories is not something that I'm going to get too involved with, because I still want to back to the fact that if you have this particular population of people, many of whom will be able to actually consent to research. The reason one puts a protection in place for them is, if during the research they should become psychotic, then you want these protections in place because that's when they will lose their decision-making ability. And so, if you identify this with the population and their minimal risk is their everyday minimal risk, that part of that risk is that they will have a psychotic episode. And you, willy nilly, however you identify whatever the other risk is going to be in terms of the research, you must have these other protections in place.

DR. SHAPIRO: Thank you. Let me just make one comment, Jim, then we'll go on. I find myself in reacting to this type of material to want to be somewhat conservative. That's what, Alta, your position was or is, if I understood, regarding exposing this population to risk. But it doesn't seem to me, Jim, in the end, that the real issue is whether there are two categories or three. It's a hugely textured situation, there are thousands of categories or millions of categories; two versus three hardly makes any impact on the problem. The problem, what that tells me, is that the problem is somewhere else and not whether we have two or three. That may, I don't think that's a big issue whether we have two or three. But the issue is what protections, I guess that's what we're going to next, really apply as we go ahead with either two or three. So I think it's a useful suggestion you made that we move on to think about those things and come back and view where we are in this issue.

DR. CHILDRESS: All right. Let's start with one that builds on our discussion yesterday with Professor Saks, and that is methodology for assessing decision-making capacity. This is in your draft, it appears on 153, it also appears on 148. And the recommendation here is that IRBs should not approve research protocols involving persons with questionable decision-making capacity, again with the language we changed, without a description of the methodology that will be used in assessing potential subject's capacity. On 153, "this requirement does not apply to minimal risk proposals," and this is why the other category is important as to what will be triggered, and so, now, if we're talking about more than minimal risk categories the proposal in the draft is that the methodology be spelled out. Now obviously that's not requiring a particular methodology, it's not indicating to IRBs how they need to assess it.

DR. SHAPIRO: Alex?

MR. CAPRON: A question. I have understood that everything, from 147 on, is more than minimal risk.

DR. CHILDRESS: That is the way we have stated it here. However, I would note that given the way that this is structured, there are a couple that may well be applicable elsewhere, for example, apparent dissent.

MR. CAPRON: And IRB membership.

DR. CHILDRESS: And IRB membership, that's right.

MR. CAPRON: I was going to raise that as a question about the structure, and did Jonathan write it off?

DR. CHILDRESS: No, and I think that's right, that submerged and that will need to be taken care of.

MR. CAPRON: Well on the specific point here, I believe that if we are talking then about the more than minimal risk category, that we should say, in addition to the methodology, that this be applied by someone other than the researcher. The subjectivity that Professor Saks was talking about yesterday is unavoidable in any case, but it is certainly more problematic when the researcher is making those judgments and doing the scoring, and so forth. So, it would seem to me that we ought to add to the regulation.

DR. SHAPIRO: Alta, Eric, then Bernie.

MS. CHARO: First I second Alex's motion. Second, it seems to me that it's not solely the subject's capacity that one is trying to measure before the enrollment is completed—it's their comprehension. Going back again to Arturo's comment about the betrayal that people perceive from feeling they've been deceived. I think in this population we have a classic problem with all human subjects multiplied, which is an absence of clear comprehension and retention about what it is that they've now embarked upon. And then if at the very end you suddenly rediscover that you've been a subject or you rediscover the absence of benefits or you rediscover the side effects, you really do feel betrayed, and that is something we don't want people to experience. Whether or not the betrayal is real or is only in their minds, we don't want people to experience that. So I'd like very much to add something about an independent assessment of their comprehension and retention of that information. At least in this population, even though it might be a good idea for everybody.

DR. SHAPIRO: Eric?

DR. CASSELL: This may seem minor, but I would like the word "methodology" to come out of there. I think it should be with a description of how the person's potential, potential subject's capacity is to be assessed. Because if I heard anything yesterday I heard there is no methodology for doing that.

DR. SHAPIRO: Could I just ask a point of information on this issue? When I read the language that's actually in the report right now, Jim, it seemed to me like someone was supposed to describe what they were doing as if that, by itself, was sufficient, it seems to me. But if what is implied is that the IRB would at some sense assess this or feel it's adequate, even though not uniquely adequate, that sense of it was important as I read through it. You simply have to describe it, it seems to be not even in it, a requirement. But that may be implied, so it's just a question.

DR. CHILDRESS: It was meant to be implied. I think that it will be clarified to make sure that it's understood. If I understood, Harold, it just says IRBs should not approve research protocols without a description of the methodology being used; that is, the research protocols have to have that description. But there's nothing, the implicit point is that the IRBs then in some way will assess what is proposed, and that's not stated here.

DR. CASSELL: Yes. Because that's part of the educational value of the IRB.

DR. SHAPIRO: It seems to me, Bernie and Eric, did you want to say something? Bernie?

DR. LO: Harold anticipated what I was going to start saying. I think it needs to be much more explicit, because there are other requirements that you just have to fill in the blanks. And just, people make sure not .... The ethics section of most protocols that go for most IRBs is often that way. But then I think we have to address the question, I don't know, maybe you discussed this yesterday when I wasn't here. But again, we're putting then on the IRB a very, very serious responsibility beyond what they now are doing. And real questions about do they have the expertise, even if we add in two additional members who may also be patient or family advocates, do they have the time to do this, and so forth. So I think that we want to move in this direction, but I really think we need to think about the practicalities of whether writing it as an IRB requirement will really do anything other than just have another bureaucratic requirement.

DR. SHAPIRO: Eric?

DR. MESLIN: Just very quickly, and Alex and Bernie have echoed the point. Jonathan and I, again I'm sharing with you my plane conversation with him yesterday in his absence, and in discussing that one of the ways that he was thinking through it was that an IRB need not be required to assess capacity itself, for all the reasons that Bernie has suggested could be problematic. But that an IRB could require that it be assured by investigators that capacity is going to be assessed, and a description thereof. And that's where the ambiguity of item three comes out. If you just simply say, "Tell us that you're going to do it," that might not give the Commissioners the feeling of confidence that this recommendation would be carried out. Another way of looking at it is to require IRBs to require of investigators that they assure the IRB. And the regs permit IRBs to bring in other experts who have the expertise to assess various aspects of a protocol that is not represented in the membership of that particular committee at that time.

DR. SHAPIRO: Trish

MS. BACKLAR: The problem is that as soon as we start to look at any of these particular categories one sees all kinds of pitfalls all over again. And that is, I become concerned about manipulation of consent and even if you've got the methodology or how you've used it. So one wants immediately, right here, to be able to put in protections for a vulnerable population, and that's what we're looking at, vulnerable populations and people who have decision-making incapacities, whether it's permanent or fluctuating. And I think one of the interesting suggestions from Ducoff and Sunderland was that a surrogate is appointed, and that the surrogate participate in the informed consent process so that the person who may lose their capacity at some time further down the road in the research protocol. The point is that again, we want to look at this to think about what are those extra protections that you may want to be putting in place right at this initial point.

DR. SHAPIRO: Alex?

MR. CAPRON: I want to see if I understood the, I'm taking a step back, I'm afraid, to the Chairman's comment. Would something along the following lines be what we have in mind under point three? IRBs should not approve research protocols involving persons with, or whatever language we're going to use there, decision-making capacity, unless they are satisfied that an adequate and appropriate method will be employed by a competent expert who is independent of the research team to assess the potential subject's capacity, or decision-making capacity. And we're trying to be quite specific about this.

DR. SHAPIRO: That, all I can say is that's what I had in mind. I hadn't thought of the exact language here at all, but...

MR. CAPRON: But that's what you were trying to...

DR. SHAPIRO: That was the kind of thing that I had in mind. Diane?

DR. SCOTT-JONES: Are we concerned for a specific research project with the subject's capacity or their comprehension of that particular study? Because there aren't going to be good ways of assessing capacity in general that could be easily incorporated into a piece of research. But you could probably more easily assess whether someone has in some way comprehended what you're presenting to them at a particular point in time, but to assess something called capacity or ability is going to be extraordinarily hard to do.

DR. CHILDRESS: That's understood in a specific way here, the capacity or ability to be able to understand information and make a judgment about participation. They did, when we use the language, and it's going back maybe to the earlier point, I think you understand capacity and ability in a very global sense and enduring over time. But actually, in many discussions such as this area, it's not always understood that way, it's understood often as limited, that the ability to do something kinds of things, it's task-oriented rather than global...and that's what's understood here. At least that's the way I'm understanding the language here.

MS. BACKLAR: Right. And like the Berg and Appelbaum paper on assessing capacity....

DR. CHILDRESS: ...and that should be clear here. I think that that would help address the concern that you've raised because it's sort of implicit in relation to Harold's point. But it could be stated more clearly here. Arturo?

DR. BRITO: A point of clarification, Alex, from your definition or your changing of the language here. We're talking about appointing an independent person, requiring appointment of an independent individual, right, for measuring this capacity. That's what you said.

MR. CAPRON: Right.

DR. BRITO: Okay.

MR. CAPRON: I mean, the idea would be....

DR. BRITO: That's the key, I mean....

MR. CAPRON: The idea would be your research protocol should specify that the subjects that you propose to recruit will be evaluated by someone who has the ability to use something—various instruments that we heard about or whatever—and, that that person is, as Diane just said, assessing...I tried to add in her idea here—the potential subject's capacity to decide whether to participate in the research...

DR. BRITO: Right—even though there's not a standard way of doing it, or necessarily an accurate way. At least if you have...it's an added benefit; it added protection by having somebody independent do it.

MR. CAPRON: What I think we're saying in all of this is if these regulations are implemented by conscientious IRBs, they will be flagged to them that this

is a point of concern. The very question of whether you have the capacity or not may influence whether or not you can be in the research and/or influence whether someone else can enroll you in the research because *they* think you should be in the research. And, I mean, the kinds of examples that Trish was reminding us of, and I think you were right to remind us, it isn't just people who are in institutions at that the moment that the research begins, it's the prospect: If you'll sign your son up for our research we'll let him into our institution and you can get a good week's sleep. I mean—it can be—in so many words that could be what's at issue. And, if we then say that the person that's going to make the decision is that desperate relative, the protection that that loving but desperate family member is giving doesn't amount to what we thought it amounted to, which is why Alta is right to remind us. And, until the last 15 or 20 years, the law at least was fairly clear that for anything that was not designed to—and, you're right, it doesn't always benefit—but wasn't designed to be of therapeutic benefit for an incompetent person, no one else could consent to that person being involved—save, perhaps, a court with a full hearing and everything. But the notion that just because you're the surrogate, if you take your child in for treatment and the doctor says, "Well, we don't have any very good treatment but we have an experimental treatment," that you could say yes to that, and then the doctor says, "But I'd like to enroll him in research that isn't connected to any benefit to him, it's just that I want to study something," you didn't have the ability, the legal authority to consent to that in the past. And we've slid a little over—say, well, if it's only minimal, you know—I mean, what's wrong with weighing a baby or looking at its eyes when it's newborn, or—you know—doing things like this. It's not going to hurt the baby. Sure, parents should be able to say. We've slid into that, but then the question is is that surrogate consenting to more and more and more.

And, this is the fulcrum at which that turns because if you have capacity you make the decision for yourself; if you don't, then we're saying someone else is going to make it for you. So it's the key thing on which a lot of this turns.

DR. CHILDRESS: I think that's—that's right. I'm hearing, I believe, the general consensus about a direction for this with some of the wording ... and that'll be worked on, but is there any strong opposition to this direction?

DR. CASSELL: Would you state what you believe to be the direction?

DR. CHILDRESS: Basically, it's captured in Alex's formulation. The only issue that remains, or one of the issues that remains, is whether we want to stick with this in terms of not applying for minimal risk proposals. That seems to me to be something we've not talked about in relation to....

DR. CASSELL: Might I hear it as a whole paragraph?

DR. CHILDRESS: Okay. It takes off from the present language of number 3. "IRBs should not approve research protocols involving persons with questionable decision-making capacity unless they are satisfied that an adequate and appropriate method will be employed by a competent expert who's independent of the research team to assess the potential subject's capacity to decide whether to participate in the research."

DR. CASSELL: My only problem with that is that the emphasis is on method as well as on third parties, and that makes me nervous.

DR. CHILDRESS: In what way does that make you nervous?

DR. CASSELL: Well, because somebody comes into the IRB and says, "We're going to have our third—I mean, our independent expert administer the Applebaum thing, the IRB," and they say, "Well, is that an adequate method," and they say, "That's in all the literature, it's the only one in the literature," and we know it not to be good. It's the method that bothers me.

MR. CAPRON: Well, one thing I think we're going to try to do in the report, which isn't yet reflected in it, is take some account of the kinds of concerns that were—will be more fully fleshed out in writing by Professor Saks, at least to flag for people what methods are out there and what concerns they might have as to whether those methods address the very questions that are most essential. For example, the one she was talking about yesterday, volition and authenticity. It may not be in there. You may be concerned to say in that case if this is—if this is really risky research, we're not comfortable with that method being inadequate on the point of volition. If people are being drawn into it who are delusional and who believe themselves to be compelled to do things, you'd better make sure you use some method that looks at their delusions and their compulsions to see whether they're saying, "Yes, I understand that and I agree and I can evaluate the risk" and so forth is reasonable.

DR. CASSELL: Do you think the IRB has the capacity to make those decisions?

MR. CAPRON: That gets to Alta's other suggestion, which is that some at point should we be talking about national or regional bodies that have more expertise than an individual hospital IRB. And that's, I think, a very good question that we had; it's a method we hadn't talked about before.

DR. SHAPIRO: Okay. This—Bernie, do you have a comment? Because then Jim wants to get us to the next point.

DR. LO: Right. I just want to make a quick comment, that see, this to me is the kind of example where it would make a difference how much more protection I would want to put into it given protocol, all the other factors we talked about this morning, so that if the more-than-minimal-risk is a PET scan, I'm not sure I would want an outside expert to review the methodology and have it go to a regional committee. But if it was an experimental drug, that wasn't directly, I mean, it just seems to me the type of protection you put in isn't just captured by the sort of level...

DR. SHAPIRO: Okay, Jim did you want to—before—also, Trish has some remarks to make, but let me turn to you first.

DR. CHILDRESS: Okay, on the point about the method for doing this, you'll notice also on 152 that there's a recommendation that NIH sponsor research, that can extend knowledge concerning the most reliable methodologies—sorry for that word again, Eric. And this is one recommendation that's been added to the report, that this is an important area of research.

DR. SHAPIRO: Alta, then Trish.

MS. BACKLAR: Oh, it's all right. Alex, really—I just wanted to respond to what Bernie said because it depends, again, on the population. A PET scan may be a very difficult situation for somebody who is having a psychotic episode.

MS. CHARO: I want to make sure that I'm understanding. Now I feel like I'm muddling. I thought that the purpose of item 3 was to ensure a proper distinction between the people who will be consenting for themselves and the people for whom consent would have to be sought from others. In that sense, it doesn't matter whether it's minimal or non-minimal. It doesn't matter what additional protections are at issue. It's a first-cut question of how to characterize the situation we're in, right? And, if that'd be—okay, in that case...in some ways, Bernie, I think your comment may be premature. And somebody else asked, "Does this apply to minimal risk?" and I think the correct answer would be yes...

DR. CHILDRESS: Right.

MS. CHARO: ...because we're still just trying to find out if the person can give consent. Okay.

MR. CAPRON: It's really the consent stuff that's different, before you get beyond it.

DR. SHAPIRO: Let me suggest that we take up—we stop our discussion of this; we'll begin again very shortly on this entire report. There are two issues, however, I want to take up now. The second one is we'll take a break. That'll happen in a few minutes. The first one is a letter, a proposed letter, which I think you all have a copy of, which deals with a letter which I proposed to send to President Clinton regarding the whole set of issues that are swirling once again regarding the cloning of human beings using the techniques that we tried to take a look at very carefully some months ago. As many of you know, there's increased interest in this area, both in the Congress and elsewhere, and the sole purpose of this letter is just, again, to ask the President directly whether we could be of any assistance in dealing with the situation that's currently evolving. It has no other purpose. It's not meant to reinforce exactly what we think and believe or anything of that nature, and this was a suggestion from Alex yesterday, which I, myself, find to be a very good idea. And I would like to send this letter. David pointed out to me this morning—Dave and Bette pointed out this morning asking whether the FDA, which *appears* to be about to declare its authority—my understanding is that it hasn't actually done so yet but it appears about ready to do. Whether that changes things—well, obviously it has some impact. I, myself, prefer not to mention it here, it just raises another issue. If we're going to be of some assistance, that issue will come to us at the appropriate time and so on. That's my sense of it. But, David—you know, we had a brief talk about this this morning.

DR. COX: We read the letter after speaking with you. It's phrased in such a way that I'm comfortable with sending it as it is, and it was my understanding that the FDA had gotten the authority, but if they haven't for sure, then absolutely you don't want to incorporate that in. So...

DR. SHAPIRO: So, if there's no objection to this, we will send it off. But if there' is an objection, now's the time to say so. Okay. Rachel....

MS. LEVINSON: Not an objection, but a suggestion perhaps that you also send it to Congress—to members of Congress, addressed to them—specifically the leadership and perhaps any other member that you think would be important.

DR. SHAPIRO: That would be fine. Please—maybe, Eric, you and Rachel and others could get together and decide who should be on that list, and I think that's a good suggestion. Is that all right with you? Okay, thank you very much. Let's take a break now and reassemble in about 15 minutes.

[BREAK, 10:00 A.M.]

DR. SHAPIRO: Let me remind Commissioners that we do have five or

six people or seven in public comment, which means we're going to have to allow 40, 45 minutes for that. That might mean our afternoon schedule shifts 10 minutes or so, depending on how long we take for lunch. But, depending on our discussions also, if they seem to be wrapping up a little before 12 we could stop early; if not, we'll pick it up later. So, let me turn to Jim to continue our discussion.

DR. CHILDRESS: Let me pick up where we finished, and let me just make sure now that we've got a general agreement that this particular method for assessing decision-making capacity, that this is one that applies across the board, and then the issues about minimal versus greater-than-minimal risk research will come into play after that. So, we're getting rid of the segment—the parenthetical statement on 3. That's how I understood our discussion to go, though we really didn't elaborate on that.

DR. SHAPIRO: Bernie.

DR. LO: Could I ask a clarification question on 153? We twice talk about something not applying to proposal: observational and epidemiologic studies with anonymous data. I'm not quite sure what we're talking about here. Are we talking about preexisting—review of preexisting medical records, or are we talking about actually observing day-to-day—the day-to-day life of someone with depression or schizophrenia? To me they're very different sorts of things, and I'm not sure that putting observational epidemiologic....

DR. CHILDRESS: And this is one place I'm not sure—unless some Commissioners worked with Jonathan on that particular wording I'm not sure how that originated. So, I'm sorry, I can't....

MS. CHARO: Bernie, I can say, though, that if you look at the regulations in 45 CFR about when it is that informed consent is not needed so therefore the issue of capacity is not relevant because you're not going to be seeking consent. It would be for unidentifiable data collection by observation or record review.

DR. LO: Right, but then the issue...

MS. CHARO: That's minimal risk.

DR. LO: ...the issue, then, for us is—given all that we've said about how the risk to someone who has a condition like schizophrenia may be very different than the risk to someone who doesn't. Just being observed may be more risky in some senses that it needs to be thought about and looked at, even if it's going to be anonyized data.

DR. CHILDRESS: I think that's true, and actually this would not be the place for any of that to be dealt with back in our discussion of minimal risk.

MR. CAPRON: What's the purpose of the stuff on page 153. I mean, the previous pages are so short that....

DR. CHILDRESS: This was just, I think, added as a brief summary. It's not something that would be in the report in the way it is. What we're trying to do now is work out the recommendations, and I think that Chapters 6 and 7 need to be totally redone in a way that will both sharpen the recommendations but also provide the supporting texture for the....

MR. CAPRON: Wherever we are on this question, what is the status of that parenthetical? Have we dropped it now?

DR. CHILDRESS: Yes.

MR. CAPRON: Okay.

DR. CHILDRESS: It's my understanding....

MR. CAPRON: Substantively, not just—I mean...right. We're saying could we go through each of the major points—IRB membership, assessment...

DR. CHILDRESS: That's the plan. Go through each of the sections, so as soon as we finish this one we'll go to the next one.

MR. CAPRON: But we jumped over 1 and 2.

DR. CHILDRESS: Yes, but that was to connect with our discussion yesterday, that this particular order here makes no difference in terms of....

MR. CAPRON: You *are* going to go through them all.

DR. CHILDRESS: Yes. I'm going to go through each one of them. Not only those, but the ones that appear and are not summarized as well. And we're going to turn to IRB membership after there's no further discussion of this. And let me get—though Steve had a point I'd like for him just to get out before us, mentioned it in passing out in the hall, about his visual conceptualization of where we are in terms of thinking about protections in relation to the other categories. Steve, you want to make that observation, and then we'll turn to IRB membership?

MR. HOLTZMAN: And, again, I don't know if it's useful; it may very obvious. Just sitting and listening, it seems to me there are three different kinds of issues we're dealing with. The first is: what is the objective mechanism that we're trying to institute that can conclude with respect to the subject whether or not they are capable of consent, which is the point, I think, that Alta just made, that that's the number 3. What is the decision-making capacity of the individual?

The second is, what is the mechanism by which we make the determination as to where the particular study lies with respect to the potential benefit and inherent risk of the study? That will always be very, very contextual. You're not going to be able to define what in all cases is a potential benefit, what is the level of risk. It's a spectrum, so that means you need a mechanism by which we believe will provide the best judgment as to where it lies on the spectrum.

And the third is, once you have the determination of where it lies on the spectrum, what or who has and what are the conditions under which one without or lacking decision-making capacity may be involved in such a research project and laying that all out and whether or not there is a line below which on that spectrum an individual may not be put into a study without their being able to consent?

MS. CHARO: Or even with consent. I mean, number 2 is ordinarily handled by IRBs. That's the existing mechanism. They determine whether or not the risk-benefit ratio is just fine.

MR. HOLTZMAN: We may be saying that given the current constitution of IRBs that we want a better mechanism for engaging the richness of the context in making those determination of where it lost.

MS. CHARO: Sure, but that's—I mean, that's the existing mechanism. There *is* one in existence, even if we decide it's not—but, you've got to remember with number 3 that there are limits even on what individuals can competently consent to do. For example, I am not going to be permitted to enroll in research even with my full knowledge and consent whose risks outweigh their benefits according to the ratio established by the IRB. That research simply is not permitted to go forward, even if I'd like to participate. So, we routinely exercise a great degree of parentalism even over competent people.

MR. HOLTZMAN: Okay. I read Laurie's where the rubber keeps seeming to hit the road on that is where we're going to draw the line with respect to the those individuals who can't consent. Right?

MS. CHARO: Right.

DR. CHILDRESS: Thanks, Steve. Let's turn to the IRB membership question. This is discussed on 123, 124. It appears on 153. And then we have Laurie's proposed addition here that is on the materials from her e-mail message and a copy of that was circulated this morning. "All IRBs that regularly consider proposals involving persons from this population should include at least two members who are familiar with the concerns of those with decisional impairments. And these members should be present and voting when such proposals are being discussed." And Laurie's proposed condition was that one of those—at least one of those members speak from the patient's subject group or family—population. So, let's discuss that.

MS. BACKLAR: I didn't have any difficulty with that suggestion. I mean, I think it's fine to add a family member or a member of what would be a subject in that population being studied. It may be a little difficult if you have somebody with advanced Alzheimer's, so it would have to be a family member. I mean, you'd have to make that choice. Somebody with schizophrenia you could have a consumer.

DR. SHAPIRO: Bernie? Alta, do you have a question?

MS. CHARO: Point on this, but....

DR. SHAPIRO: Okay, Bernie, then I'll....

DR. LO: I like the suggestion. I'm not sure it goes far enough if we limit it to IRBs that regularly consider these types of research proposals. I mean, if you think about the protection of the subject, it doesn't matter whether the IRBs, you know, a lot or just this one. The concern is whether some input from people knowledgeable about these conditions and have a family perspective has been brought into that IRB decision making, so I think it should be tied to the proposal under consideration, not the sort of frequency with which these things come before a particular IRB.

DR. CHILDRESS: I agree pretty strongly with that.

DR. SHAPIRO: I don't know. I haven't done the language, Jim, but I think that Bernie's point is an excellent one. Alta?

MS. CHARO: And this is very much in that vein. Because as phrased, there would then be confusion about what constitutes "regularly considers." But if one wants to require some degree of input from a family member or other people familiar with these conditions every time a protocol like this comes up, then there is a second

operational question: Do you want to require that they be voting members of the IRB or do you simply want to require that a consult be taken with these people? To require that they become regular members of the IRB does in fact affect the membership of the IRB on a permanent basis, which is why I suspect this original language of "regularly considers" was put in; otherwise, it might take away a slot for something like a pharmacologist or whatever that you need as well. On the other hand, to have somebody only give a consult without voting authority reduces their ability to play that protective role. So, some small attention to exactly how urgent we think this is and how we then want to implement it is I think appropriate.

DR. SHAPIRO: Steve.

MR. HOLTZMAN: So, question—how the law, if you will, on IRBs, and again I'm totally ignorant—does it specify a kind of membership whereas there is a provision that could say you could have a core membership in an IRB, and then there are additional slots—which are voting—which one would bring in.

MS. CHARO: There are rules that govern how it is that IRBs are constructed and rules about their voting and they can be kind—we've now got a new IRB administrator who's *very* picky about our rules because she's an OPRR veteran, and I've discovered that they're extremely specific. So, you could not simply have people who come in on certain protocols and become voting members and then vanish. That's not going to be permissible. You *can* have consults. That's no problem. But then you'd have to rely on the members of the IRB to take those consults seriously and use that information.

DR. SHAPIRO: I think we may have lost the.... I think that our P.A. system may be zapped.

MR. CAPRON: I think so.

MS. CHARO: You know, if we wait long enough we might just float to Hawaii and we'll be able to see Larry in person. [GROUP LAUGHTER]

DR. SHAPIRO: Trish. For the moment, while we're short of—please, let's continue our discussion because I don't want to adjourn, but please, people, raise your voices and talk a little slower so that people—we can communicate a bit.

MR. CAPRON: How will we have a transcript?

DR. SHAPIRO: Rob's going to type it all in.

DR. MESLIN: Are you able to hear us?

MS. PADDOCK: Yes.

DR. MESLIN: Okay. We'll do our best, and Robert's taking notes, although they aren't verbatim.

DR. SHAPIRO: Trish.

MS. BACKLAR: I don't want to add something that is more complicated, but what might be interesting to consider in this kind of situation is that almost every state has an advocacy center, advocates for people who have difficulty with decision making. Certainly, I know we have such an organization in Oregon, and it might be useful not simply to suggest that families or subjects, but also that gives one another opportunity for somebody who—for representation for the group. So one might want to say an advocate—patient advocate.

DR. SHAPIRO: Tom?

DR. MURRAY: I think we have a very, just a pragmatic issue here, right? And, would it be appropriate to say something like this, and nothing hangs in the specific language, that all protocols involving these—populations such as these need to have some consultation with people familiar—and then we could use the language. And then all IRBs that regularly consider protocols involving such persons ought to have voting members as we've just—as specified here and, as Laurie added, a family member where possible, or—or a person with a disorder. Is that possible you think? Alta, given your understanding of the regs, can we...?

MS. CHARO: It's absolutely possible. I mean, we'd want to have some way of getting a sense of what "regularly considers" means or the IRBs themselves simply won't know whether or not they ought to be doing this. And then it would be up to OPRR and its assurance program to make sure that the IRBs are implementing that should this ever rise to the regulatory level. But it's certainly doable.

DR. MURRAY: I'm simply trying to articulate what I think it says.

MS. CHARO: The irony—without—the irony, though, of course, is that it would mean that the IRBs that are least familiar with these kinds of protocols would be the ones who have the weakest protection in the sense of not having the one familiar party being a voting member, if you catch my drift, which is kind of....

DR. MURRAY: But it's also—be the—the fewest studies would come to those IRBs.

MS. CHARO: Well, that's the point of not "regularly considers." Yes. Whether or not they have the fewest—they probably have the fewest subjects.

MR. CAPRON: It depends on how Machiavellian you are. I mean, if you're a person who finds that this newly enhanced IRB at the State mental hospital is giving you trouble but if you waltz around to a dozen different private hospitals that don't do very much research, you can persuade them to let you have access to their patients who are being treated for mental disorders, and they have no one on their IRB because they don't regularly consider this and when you come in and said this is all just hunky-dory wonderful stuff, there's no one there to say, "Wait a second, we know that people in this situation react differently to these kinds of stresses and it's riskier than you think," or whatever.

DR. MURRAY: Yes. So what do you propose, Alex?

MR. CAPRON: Well, I think it—I have no problem, and there isn't—Alta's always much more knowledgeable about the regulations, but there is a provision in regulations in other settings for ad hoc members of the IRB, right? And I see no harm in saying either—if they consider—regularly consider such work, they should have regular members and if not they should have an ad hoc member appointed.

MS. CHARO: No, that's what I'm not sure is that they have provisions for ad hoc members as opposed to consults.

MR. CAPRON: Ad hoc participants, is that what it is?

MS. CHARO: Yes, but they're non-voting. I remember—if I remember correctly, you know—frankly, I'm not sure that the voting makes a difference.

MR. CAPRON: I don't think the voting makes a difference. I mean, and if you really got a decent advocate who sat in the room, gave good arguments, everybody at the IRB was, you know, insensitive to those arguments, that person leaves the room, picks up the phone, and calls the head of the institution and says, "I have problems with what I just participated in and if you go forward I plan to file a complaint that these concerns were not taken seriously. I'm an advocate for these people and you just have totally—I was window dressing. Made no difference. No one discussed it and they voted on it as though I weren't there." I don't think that's the dynamic of the IRB, that if the person is there and raises serious concerns, they've got to persuade the

majority in any case, even if they had a vote it would only be one vote. So, I think the notion you have someone in the room who can say, "Look, that sounds fine, but with this population you've got to have different concerns." Whatever the population is, whatever the research is. Or who says, "Actually, the concerns you're raising are the wrong ones and this research should go ahead because blah-blah-blah it's important." I mean, whichever—they bring some expertise to people who might otherwise just be looking at diabetic studies or whatever.

DR. CHILDRESS: Being conscious of the time, are there other points on this?

DR. SHAPIRO: "This" being what?

DR. CHILDRESS: These IRB memberships.

DR. SHAPIRO: Yeah, I want to make a point just to get something that's been on my mind for a long time. I've mentioned to a few people—everyone I mention it to thinks it's extremely unwise and a bad idea [GROUP LAUGHTER] so far.

MR. CAPRON: You want to hear that from more people. [GROUP LAUGHTER]

DR. SHAPIRO: I want to hear it from more people. I'm masochistic in this sense. When I read through this material and began to try to think about this and thinking of all the issues that have come up, I reminded myself that the key criticism or concern we get about the IRBs all the time is that they're overworked, that they can't really bring—there's aren't enough time to bring enough thoughtful judgment to bear on very difficult, sophisticated issues in this area for example—other areas as well, but certainly in this area. I then married that observation in my mind with another assessment, namely that typically MDs get little to no training in psychiatry if they're not becoming psychiatrists, and asked myself who's going to be sitting on these IRBs that can really give a very thoughtful analysis of all those difficult issues that we're talking about today. And I said, oh well, there's a simple solution to that, namely, have a separate IRB for dealing with protocols in this particular area, dealing with this population, thereby assuring that you have enough expertise and thoughtfulness dealing with these issues. Now, when I mention this, for example—I think I mentioned it to Eric—he said, well, what's—you know, not quite what else is new, but the—what about other diseases. You could make a similar argument, I think, with respect to other categories. That's probably true, one could. And, I don't have a good argument for making this separate as opposed to cardiovascular disease or pick out another large disease—cancer protocols of one kind or another. And I think that that's—maybe that's

just enough to settle that issue. So I just mentioned it, not because I'm going to push it because it doesn't seem, as I mentioned, around to getting the residents anywhere. But I should say that in my own mind it resolved a number of issues for me. I don't want to spend a lot of time on this cause we may be not going anywhere close to this. But maybe if there are one or two responses to keep me quiet and send me back to thinking about something else, that would be good.

DR. CASSELL: I think that the point about it is that it addresses some concerns that if they aren't addressed, then we're going to continue to have trouble with this kind of protocol all along, whether that—whether creating a new IRB and an IRB administration, I just have a picture of this at Cornell and it would have problems. But, I want to say, first of all, it is *not* the same as cardiovascular disease, cancer, and so forth. It's not the same as that. This is a different class of problems. It's a different class of research subjects. So, that's not a cogent objection to it. The fact that the IRB is overwhelmed—I think that we're going to address that. I hope we're going to lift a lot of administrative junk off their desks so that they can concentrate on this by giving them alternate solutions to the other problems. So, ultimately I think, although I don't believe this is the best way to go about it, I think that we have to address the issues that you're addressing. They have to be addressed; otherwise, all of this is meaningless.

DR. SHAPIRO: Alta.

MS. CHARO: Yes. I mean, I'm slightly more enamored at the suggestion than Eric is, but I recognize that in some institutions it may not be possible. But, if you're not you ought to be aware that there's nothing that stops an institution from doing this now.

And, most institutions do have multiple IRBs for different areas and for sure we could mention that institutions that regularly consider this kind of research with substantial numbers of protocols should consider forming an IRB that focuses specifically on them in case that it never occurred to them to separate it this way. And if they've got the expertise and the capacity to do it, it's—actually I think it's an excellent idea.

DR. SHAPIRO: Trish? Tom?

DR. MURRAY: I think it—second what Alta said. But also it solves the problem where it's least likely to occur, given our current recommendations, and doesn't solve the—creates new problems where you've got institutions that infrequently do research—have research protocols for persons in these categories. So, where you've already got a lot of it going on you could have your own brand new IRBs specifically

directed to towards it, or we would say you need to have at least two members of the voting members who are experts anyway.

DR. CHILDRESS: We're basically reversing that and saying that in order to make the requirement of the two additional members and then if you're doing enough of these you might want to consider the other....

DR. SHAPIRO: Right. Trish.

MS. BACKLAR: But, actually—well, that still does not necessarily ensure adequate protection. I'm thinking of the schizophrenia research at UCLA, which had, apparently, a psychiatrist and a psychologist on the IRB.

DR. CHILDRESS: Nothing can—*nothing* can ensure adequate protection, okay. The question we have to ask is whether given the current state of affairs is it better to go the direction of putting in place some of these things? That's our—we're not going to have perfect protection.

MR. CAPRON: Where do we come out on this? Are we saying a patient, a family member, or a member of an advocacy organization.

DR. CHILDRESS: We did not resolve that. At least one of the two should be from that category. We, we--Alex, let's take that at a proposal.

MR. CAPRON: I propose that we say that at least one of the two should be either a person from this population, a family member of such a person, or an advocate from a—or a representative of a patient advocacy organization.

DR. CHILDRESS: Is there any objection to that? I'm conscious—actually I'm trying to push some things pretty fast because what we need to do is get a sense of where people stand on a variety of these protections so we can come up with another draft.

DR. SHAPIRO: Bette.

MS. KRAMER: These FDA information sheets that we have, on page 6, say that an ad hoc substitute cannot vote, but they refer to alternate members who *can* vote, so that might be a way to go.

MS. CHARO: Just by way of information, alternates are basically people who come when the regular member is out of town or sick or they're, they're...backups

for one another. They're somebody else in law who backs me up if I'm out of town on the day of the IRB'S meeting.

DR. CHILDRESS: Okay. Have we gone far enough on this? If so, let's turn to the question of limitation of research. This is number 2 on 153; it's also discussed on pages 123 and 24. "No research is permissible with persons who are decision-impaired or whose capacity is questionable in categories when the research can be done with other subjects." Now, a few questions have arisen about that. Laurie, I think....

DR. SHAPIRO: I think it's true that one of the issues that Laurie picks up in her memo has a little different perspective on it. It's reflected in this draft, but the question is how do we feel about it, and how do we feel about what is sort of an outright limitation, at least as described this way. How do people feel about it?

DR. CHILDRESS: Well, my reaction is positive to it simply because the—while, of course there's a cost to everything that has a constraint on it, that the—going the other way was much more dangerous and so that it seemed to me that they just deserve the protections, so I'm satisfied, not in principle the way it's written—not—I haven't looked at the language with all the care I need to, but....

Why don't we ask it this way then. Is there any objection to this; if not, we'll move on to....

DR. MURRAY: I just want to clarify, Jim—if I understand what Laurie's saying here, suppose my daughter has profound schizophrenia so she's not, whatever, not able to make a decision. Also happens to have a form of cancer for which there isn't a useful treatment and the question arises, can my daughter be enrolled in a—in a experimental trial to try out this new cancer therapy? Is that—is that what I'm hearing from her?

DR. SHAPIRO: That's not what I've heard from my reading of it, no. The question was whether there is something dealing with the illness that she has is my understanding of what Laurie said. She has two illnesses. And the second...and our rule would say no, you can't involve her.

DR. SHAPIRO: I can't hear you, Trish.

MS. BACKLAR: I would say that you cannot involve her.

DR. SHAPIRO: That we *should* say that you cannot—we cannot enroll her in a trial for this new therapy for her cancer. That's what you want to say.

MS. CHARO: She could be enrolled in like a treatment IND under the FDA. I mean, if this is something in which you're really seeking to get her a benefit from, a drug or device that's in the research stages, there are ways that you might be able get access to it outside of enrolling her in a research trial. Right. Through things like treatment INDs. And treatment IDEs. But it would, in fact, preclude having her enrolled along with all the other cancer patients in that cancer trial. I don't think that's what Laurie was worried about, but it's a good thing to worry about anyway.

DR. SHAPIRO: Bernie.

DR. LO: This is an important issue. I would think about someone with HIV, where you may really only be able to get a promising new drug which is probably better than what's out on the market through a research study because of getting it through treatment IND is really not feasible in a lot of situations. And you could do a treatment of the newest protease inhibitor in people who had intact decision-making capacity, but you would leave a whole group of people for which that may actually be therapeutic. So, I'm a little troubled—I mean, I know the intent here, but I think we have to keep in mind that there are some research studies, few and far between, but certainly in oncology, AIDS, and immunology—rejection of transplants—where the experimental therapies are probably better. And people are clamoring to get into the therapies. They're not asking to be protected.

DR. CHILDRESS: Would this be a place where one could draw the line, then, between research that offers the potential of direct benefits—medical benefits—vs. the other.

MR. CAPRON: Well, it raises—the discussion has raised a bigger question for me. I sort of thought that the heading of this subpart, as it would appear in the *Federal Register* as it were, became a part of the common rule—was not solely focused around the patient but around the research, that this is really research on mental disorders, and these are special protections, for the participants in that research who are overwhelmingly going to be people *with* those mental disorders. Now, there may be some normal volunteers who are brought in for studies of comparative reasons and so forth—they may be in here, too, but they don't need special protections I guess. But, I guess I had—I mean, I had been conceiving it that way so my first reaction to Tom's thing is no, this doesn't address that because that's not what's being—the research intervention that you described was a cancer intervention, not a—if other people are thinking otherwise, that we are writing special protections for a category of patients whatever the intervention is—it's a perfectly arguable position, but if that's what we're doing, I guess I need to plug that into my thinking cap as I read all of these things, and then I would be inclined to say that we have to be more specific here and we would say

something like, “except in situations where the intervention is designed to potentially address or potentially cure or potentially whatever ameliorate a life-threatening condition.” I mean, what you’re saying is that it would be outrageous to stop someone who could, whose only chance of having an intervention is an experimental intervention for something life-saving in a situation where if we hadn’t written these rules people would say that’s the very kind of thing that that person and/or the surrogate can consent to. You have AIDS dementia—you should still be able to be treated for AIDS with a research treatment, because someone will be in a position to make that decision for you and you wouldn’t be disqualified—why should we write a rule. They’re not trying to do an experiment on dementia; they’re trying to do an experiment to stop your AIDS, the HIV virus. Have I got this all wrong?

DR. CASSELL: No, I don’t think you have it wrong; and the way it is written now it could be misinterpreted, and it should be clarified.

MR. CAPRON: But is the clarification to say what we’re talking about is research on mental disorders are we talking about a population who should be protected whatever the research is. I mean, as I say, either....

DR. MURRAY: I was clearly thinking the latter.

MR. CAPRON: Which is the latter, I’m sorry.

DR. MURRAY: That we’re talking about a population. This population, and some of the evils we wish to avoid was the use of people with impaired decisional capacity in research that has—you know, where we could be using perfectly healthy volunteer populations but where they just happen to be convenient and that’s been one of the sources of abuse. So, I was thinking population.

DR. SHAPIRO: Carol?

DR. GREIDER: As I read Laurie’s memo here and listen to some of this discussion, there’s one thing that makes me a little bit nervous, and that is equating research with therapy. And, the way I read what she is saying here is that you don’t want to exclude certain people from research protocols because those protocols might be the only therapy they have available. And, it makes me very nervous for people to assume that a therapy that is a research protocol is going to be efficacious. I realize that in practice this happens all the time, and this is a problem that we’ve heard about, and people just want to get into protocols because it’s therapy.

DR. SHAPIRO: Alta?

MS. CHARO: I was operating under the assumption all along we were dealing with the subject population like Tom, and that the first cut of protections was to make sure that they were not used because of convenience, like mentally retarded teenagers in an institution who are being used to test a new DPT vaccine because they are convenient. And, in fact, I thought Laurie's criticism was somewhat misplaced, because she was misconceiving what this protection had been about and was imagining a problem that doesn't arise. But, with regard to Tom's concern, it is true that there are going to be certain categories of illnesses for which there is no good standard therapy, and so basically there's no therapy at this point. There's crap shoot and your best crap shoot may be in a research trial. And, I'm concerned about how we write this language in order to maximally avoid the teenagers-in-the-institution problem, because that is going to be very tempting. And, you know, fortunately with HIV there's already a parallel track system that allows ineligible people to get a hold of the stuff, but in the oncology arena that doesn't exist.

DR. CHILDRESS: Could I propose that we get a couple more comments about this and then ask a couple of people to volunteer to draft language that we'll circulate and see if we can find something that will satisfy this, because I think this a very important issue. What appeared to be a very simple recommendation suddenly has complexities that I think we need to address carefully.

MS. CHARO: Especially because, if you think about it, there are some non-psychiatric illnesses that have a consequence of impairments of decision making. So we can predict—and AIDS actually was a wonderful example in that sense, AIDS dementia—that this will regularly occur in non-typically psychiatric context.

MR. HOLTZMAN: It seemed to me that Laurie's note had a number of different points and we're starting to flesh them out. And, I also wanted to know whether we feel we've addressed the concern of Steve Hyman on this point as well, and where's he dealing with—only he's dealing with the issue of...Hyman raises the issue on this that he's in line with the spirit of it, but have we worded in such a way that it's too strong, right? And, I think that's worth considering when you set aside this group. And then Laurie raises the other point about decision-making capacity, whether or not that encompasses fluctuating capacity and therefore, in laying it out this way, we've excluded those even though they may be the most appropriate for the study.

DR. SHAPIRO: Okay. Bernie and then Trish.

DR. LO: A suggestion for trying to resolve this issue of concurrent serious illness where there's a research protocol that promises some therapeutic benefits. We could let you go back and look at the language that was used for the parallel track

system so it has--it's something along the lines of life-serious, life-threatening illness for which there is no effective standard therapy, something like that, or standard therapy s inadequate, has failed in this particular case. So, I think we can go back to the precedents of where people have said these are such dire situations that we want to make sure that people have access to experimental therapies which are probably as good as or better than what else is out there.

DR. CHILDRESS: Could Bernie and Alta, Alex—anyone else who'd like to—promise to work on this and get us something in the next few days?

MS. BACKLAR: Would we want to go back to the language which said something about that they could only be in research that addressed conditions that they had? Research—in other words, if they didn't have the condition they couldn't be in the research protocol.

DR. LO: Okay, Alta's situation with immunization. They need the immunization. I think it's a serious condition for which there's no good alternative that they could get a standard therapy.

DR. MURRAY: I'm sympathetic with Jim's desire to move us forward here. I think those of us who have some ideas about how to rephrase this ought to try and share some language. And I think it's a solvable problem.

DR. SHAPIRO: Jim.

DR. CHILDRESS: Okay. Here are some in the next hour we need to hit: notification dissent, which also appears on that page—that's number 4—we'll turn to that next; the role of the legally authorized representatives, including the natural surrogate or family member; research planning, which has been one of Trish's important concerns; and then there are some others about independent health professional monitors and so forth. But I think the biggest ones we need to hit are notification dissent; legally authorized representative; and research planning. Is there general agreement that those are three that we really need to hit over the next hour, and we'll do as much more as we can? And if that's okay, then, let's start with number 4 on page 153, the notification dissent. This does appear in some other places as well, and with some inconsistencies. On 125 we say, "This will apply to all minimal and more-than-minimal-risk research." Here we have the condition at the bottom in parenthesis that we may want to eliminate, and indeed I think we should. I don't—on page 154 we have it in what we might call therapeutic research but not in the non-therapeutic research category. So, there's a lot that needs to be cleaned up in this area. But from now on let's deal with the fundamental issue. The requirement for notification, and it may not be completely connected with the

notification, the recognition of the role of dissent. Because someone might dissent to a particular procedure that's part of a research protocol, and that would be separate from the notification. So, but these are treated together here. And, let's address the issues that arise from these two proposals.

DR. SHAPIRO: Thank you. Any comments, questions, views on this issue? Bernie?

DR. LO: I'm trying to remember—I think I read something earlier in the text about requiring active assent rather than just the absence of dissent. Did I hallucinate that or is that...?

DR. CHILDRESS: Jonathan raises that in his memo that accompanies this, and there is at least one place where assent is mentioned rather than no apparent dissent. That is important issue that we need to address also. I was doing simply in terms of the formulation here but, people, if this doesn't go far enough then we may want to....

DR. LO: We just sort of raised a sort of a finely graded judgment system. Things that are much more than minimal risk. You might want to have assent rather than just absence of dissent.

DR. CASSELL: I have no problem with telling a person on my floor that, "There's a study that's going on and we think that it's difficult for you to make these kinds of decisions for yourself, but your Mom's here and she said we're going to go ahead," and then this person says, "Whatever my Mom says goes." Now it's two days later and it's the morning and the subject says, "I don't want to do this anymore. I just don't want to do it anymore." Is that the end of that project? How about that afternoon they say, "I *do* want to do it." We're talking about a population of people that something's going over time, so if we want it to be honored we have to be careful about this, because if you want a researcher to honor this instead of just blowing it away because they know that it waxes and wains and that they can be very persuasive, then we'd better figure out what we're really saying.

MS. BACKLAR: In fact, of course, that's what Paul Applebaum addresses so very well in his discussion about the MacArthur assessment of capacity. People who keep changing their minds about their choices from one time to another may not have capacity at all to make a decision, and therefore that's when you need to bring somebody else in, and certainly if they're objecting—I think we understood that any objection was going to be listened to.

DR. CHILDRESS: And this is—this is stated in some other places. For

example on 126, “even when his or her decisional capacity is in doubt,” so the possibility—the way this is worded and the supporting text would suggest that it doesn’t matter if the person descents. That is sufficient for bringing it to a halt.

DR. SHAPIRO: Alta?

MS. CHARO: You know, speaking as somebody who is inclined to be overprotective and so therefore would ordinarily go easily to the—any dissent exempts them. I think it’s worth fully appreciating exactly what this will do to the effort to do research because you will probably have a lot of people who will say “I don’t feel like it” at a lot of different moments for reasons that may or may not have to do with the research. Maybe “I don’t feel like having to leave my bedroom—my bed right now” because it’s now time to go down to the room in the hall where you’re about to sit down and do your little survey. And if you recruit a lot of people and then you have a tremendously high dropout rate, it complicates your data assessment vastly because you have to account for why people are dropping out, especially in studies where you’re looking at the acceptability of certain kinds of intervention where it’s not just doing a scan to see what level of oxygen consumption there is in some particular lobe of the brain, but it’s looking at how people react to different drug or dosage regimes or therapy regimes, so that the drop—the phenomenon of a high dropout rate has a direct impact on the “doability” of the research, and I would just urge us to be very careful here and to consider whether an extremely protective stance with regard to who can be enrolled at all if they’re not enrolling under their own volition might then free us up to say that once enrolled the declination of participation has to be expressed more consistently and more strongly before they really are removed, that it might be possible to be more protective in an another arena about getting them involved to begin with so that we have a little more play here and not necessarily dismantle a fair number of studies.

DR. SHAPIRO: My own reaction—I’m very cautious in this arena because I’m imagining forcing someone at some stage to participate in a procedure which they consider an assault on something. And while I certainly understand the difficulty it creates for research data,—all that I fully understand and appreciate—it still seems to me like a very, very difficult moment to get by. Now, I’m willing to learn, hear from others who have more experience than I in this area, but, boy, that’s—that’s a big step.

DR. CASSELL: I think you’re absolutely right, and that’s the problem. Here is somebody who says, “I won’t do this. I’m not going to do this anymore,” and they mean they aren’t going to do it but they’re going to be forced into participating because it hasn’t—it hasn’t met whatever thing we have; on the other hand, the way this is written, the “I don’t want to go down today—this is not my day—I’m not going to

go," is an apparent dissent from the research. Also, these are social settings, and dissent spreads. That kind of dissent spreads. So, on the other hand, forcing somebody to participate is—there's just nothing you can say about it that isn't bad, so it's between those issues that we have to come. And also we're trying to get a class of investigators to have respect—a kind of respect for their subjects, which—which at the present time we have some question about. And this one of those arenas where we have a chance to make that happen. If we're right and make it worse if we're careless. So I don't know—having said all that you think, well now what. I know one thing. I would not take—I would take the word "apparent" out.

DR. SHAPIRO: You'd take the—I'm sorry....

DR. CASSELL: The word "apparent." Any "apparent dissent I would take "apparent dissent" out. It's not any apparent dissent it's dissent. Refusal to—refusal to participate must be honored.

DR. SHAPIRO: Okay. Some of us have other observations. Bernie and Steve?

DR. LO: I think we need to look a little more closely at what we mean by "refusal must be honored." I mean, at first cut if someone says, "I don't want to do it" at that time, it would be morally wrong to force them to do it. However, I don't think it's wrong to come back a little later and say, "Can we talk again about this study?" Didn't want to do it—I mean, that's what we do in the clinical situation. You try and persuade. And so, you don't take them out of the study but you certainly honor their dissent at that time. Having said that, there is a danger that if everybody marches in that patient's room and badgers them, how about doing the questionnaire tomorrow or the next day, they're going to just do it to get out from under. So I think—our intention is clear, but it's complicated and we have to make sure that what's written covers both what happens just at that time, removing the person from the study entirely, and sort of pushing them into agreeing because otherwise they'll just be badgered.

DR. SHAPIRO: No, I think that's a good point, Bernie. I think it's also true if you have a rule like this, rather—my own view, rather than leading to kind of mass frustration of all research, designs will be somewhat different and we'll accommodate some of the experiences as we go along. But, in any case, that's speculative. Steve?

MR. HOLTZMAN: I would just reiterate Bernie's point and to ask Eric what distinguished dissenting for the moment from doing something versus dissenting and saying "I want out of the study." All right, if that person that you—you imagined

yourself on the ward, which I thought was great. The fact that they didn't want to do it now, but later that afternoon said, "I want to do it," did they really dissent from the study? Whereas, for three or four or five days running they said, "I don't want anything to do with this," or whatever. They've dissented from the study.

DR. SHAPIRO: Eric, then David.

DR. CASSELL: We have the problem--what Bernie says is right about the clinical setting. I've spent my life talking people into doing things they don't to do that they know they have to do. I mean, that's just the nature of clinical medicine. And-—on the other hand, there are people who don't want to do it and you *know* they don't want to do it. And there's a difference. So what is the difference? The difference is how you honor the nature of the subject. If you honor them as people who must be respected, at a certain point you stop it. You don't badger and you don't keep at them like that because that's a very powerful force. You're going to withdraw your care and all of those things. So, we're in the position, I think, of--whatever words we use, we ought to precede them with some language. The language requires the most sensitive appreciation for the subject's desire to participate at this point, the most awareness of whether they really do or really don't--because if they really don't, they shouldn't. And somehow we have to get that across. We can't write a rule and expect it to—we can have a rule but the rule has to be embedded into some language.

DR. COX: That was my point. Thank you. I guess one issue that remains, though, was raised at the outset and that is whether in at least certain types of protocols with greater-than-minimal risk, we want more than no dissent. We also want positive assent. And we need to hear a little discussion about that to guide the revision.

MR. CAPRON: I took it that the starting position is you need consent. And then the question is if it is of potential benefit, can we move down to say you can go with no assent. And it seemed to me that—I understand the problem you were having with the word "apparent," but I took it to be that that was sort of—anything that gives the appearance that the person is saying no ought to be honored rather than, "Well, they were just reluctant, they were dragging, they were saying they I'm not happy with this, but they didn't say I won't participate in research, so they didn't fail to assent." I mean, the emphasis was—I would be in favor of our continuing to say that. But my starting point was that you otherwise need consent. And the little—the chart indicates that. The chart on page 154 has, for stuff that's potentially beneficial, informed consent, including prior planning—or, no apparent dissent. And then when you get down to something which doesn't have benefit, it only allows the informed consent side. So, that's the constant part of it, and there's just this one exception—if it is potentially beneficial and someone else has enrolled you and you've been told you're enrolled and that it isn't your

decision because you don't have the capacity and you say, "I don't want to do that," "Don't take my blood" or "Don't make me stand on my head," or "Don't make me answer the question," or "I won't do that," you have to say, okay, at the least at the moment we're not going to do that, come back the next day and say, "Would you do it now?"

Just to tell you one tiny little story. Elizabeth Bouvier is a famous figure in bioethics, and of course she was hospitalized at our hospital after she came back for—when she was being allowed not to have treatment if she didn't want it. And one day her physician was greeted by a couple of frantic nurses who said, "Elizabeth is refusing to let us turn her and we've told her that if we don't she's going to get horrible bed sores and get infections and everything and should we go to court. I mean, do we need a court order?" because they don't want—and he said, "Well, let me go talk to her." And he went in he said, "Elizabeth, the nurses say they want to change the sheets and had to turn you and so forth but you're refusing to allow them to do that." And she said, "I was just watching my favorite television program. I didn't want them to do it right then." But people are so sensitive about this notion that is was just, oh, you had to get a court order in order to change the sheets. Anyway, and I don't think you want to create that situation.

DR. CHILDRESS: Could we take Bernie's last comment here and then move on to the next topic.

DR. LO: Just to say that looking at the chart on 154, to follow up on Alex's comment, the box that has potential benefit and greater-to minimal—greater-than-minimal risk is a pretty big box. And all I'm trying to suggest is that if the potential is there but it's not very likely and not very great benefit and the risk is a whole lot greater than minimum, do we want active—more active assent as opposed to no apparent dissent?

MS. CHARO: But, you should keep in mind, Bernie that if the risks are substantial and the benefit is remote, that the IRB shouldn't be permitting the research to proceed at all.

DR. LO: Well, it's still favorable, but there's really favorable and kind of more iffy, right? I mean, there's a continuum....

DR. CHILDRESS: The complexity's noted. Thank you. All right, let's turn to legally authorized representatives—their role and....

MR. CAPRON: Excuse me—before we turn, I have some other

language. I wanted to suggest two things. I wanted to just separate out the topic we just spent the last 15 minutes discussing from the question of notification, and I have a proposed revision in the notification that I'd like to suggest if I could—just to simplify it. It would say, "A conscious person who has been determined to lack capacity to consent to participate in a research protocol must be notified of that determination before a decision is made to enroll the person and must then be notified of any decision to enroll them." So, it's a two-part thing. First you have to tell them, "We've decided you can't make a decision as a research protocol and we're now—someone else is going to be asked about that." And you come back and say, "That person, your mother—you know, your court-appointed whatever, has decided that you could participate in this research." And it's connected to the other topic, but I do think we should have them under separate headings. It's connected, because to me the purpose of all that is to make clear to the person that something has been decided about them. If they're unhappy with that, they ought to let us—be triggered to let us know about it. Is that clear?

DR. CHILDRESS: Good. I'll give Jonathan that language. Please, that's a very, very good point. Thank you. Okay, two other big issues have to do with legally authorized representatives and the role of those persons, and research planning on the part of individuals often with fluctuating capacity or with respective incapacity. And for the legally authorized representatives, there's discussion in a couple of different places. One appears on 149, 127, following—I'm not sure I've noted all of them. And of course we have the chart on 154. We have also the discussion in Laurie's memo and the memo from the National Institute of Mental Health that also—both of those also address the question. So, now we're looking at issues of who else should be involved in the authorization, the participation and research, and whether an individual prior to a period in which he or she may not be able to give consent. Can we have advance planning for that.

MS. CHARO: Jim, on this one I'd like us to consider an alternative that might be simpler. The way this is phrased, it places the IRB in the role of having to figure out who the appropriate representatives are. They may or may not be the same people who've been identified under State law or under hospital policy as those who are responsible for the clinical care, and frequently clinical care and research are intertwined. So, I find this has the potential for confusion within the IRB and conflict among people with authority, and it seems that a simpler thing would be that, given the fact that we are putting constraints on what these legally authorized representatives can consent to on behalf of the subject anyway, that we simply say those people authorized under state rule or other relative rules to make clinical decisions be authorized to make these decisions whether it's minimal risk or non, potentially beneficial or not, and then we focus our energies on the constraints on their own privilege to volunteer people for research.

DR. CHILDRESS: I like that. What problems do people see with that? Any?

DR. SHAPIRO: Just to make sure I understood what you said, Alta—you want to identify this group, which is not identified here, one of the problems with this language, as that which is either stipulated by State law if that's relevant, or hospital regulations if that supersedes or there's no other—there's no State law or whatever, but some existing set of rules and regulations that identifies these people. We would just recommend using those.... They might differ by state and so on and so forth.

MS. CHARO: That's right. We'd buy into a clinical decision-maker model.

DR. SHAPIRO: I hadn't thought about that, but it sounds like a useful idea.

DR. CHILDRESS: No objection? No concerns? Great! I'm—I'm stunned, but a connected issue obviously is the research planning, and this is one that Trish has raised a lot for our discussion so let's turn to that. You can see that goes into the chart on 154 and is discussed in several places in chapters 6 and 7.

DR. SHAPIRO: Okay, are there any comments or any issues Jim has just outlined?

MS. CHARO: I'm sorry, are you on number 9 on page 150?

DR. SHAPIRO: I actually didn't think about number 9 just as one place—I didn't quite understand. In particular, I didn't understand what "incorporate the views" meant and what kind of operational significance that had. I just didn't understand it.

DR. CHILDRESS: Actually we talked about that briefly in passing earlier about that in relation to Tom's comment about involving ... two issues, and the language may be misleading here, but when we're talking about the topic right now, it's informed consent, including the planning for a period of incapacity. It's not advance planning on the part of participants, not the advance planning that could be used as seen under number 9. Research planning. It's the planning part of individuals. It's what we talked about under advanced research directives (RADs)—research advance directive....

MS. BACKLAR: You really confused me.

MR. HOLTZMAN: Jim, really, we're playing here in the case where there is informed consent and we're talking about what should be the nature and included in that informed consent in anticipation of potential fluctuating periods.

DR. CHILDRESS: Potential fluctuating or, or even permanent capacitation.

MS. BACKLAR: Actually, it's page 131 where that has been redone.

DR. CHILDRESS: And again, that's not the way that number 9—it just distinguishes this from number 9 and when they want to say more about the issue that—Harold mentioned that things may not be very clear operationally and how it didn't really work out. So we have the two separate points about planning. We now did them with the advance planning by the individual. This is also raised in—partially in Laurie's and partially in the National Institutes of Mental Health memos. Trish, do you—since this is a modification of something you that had proposed, do you want to begin our discussion in any way on this?

MS. BACKLAR: Well, I can see something on page 131 that I felt was not a good idea, and that is at the bottom of page 131, "The surrogate could be an informal care giver, a relative, or a close friend." Or the potential subject's private mental health care provider who is familiar with his symptoms that usually precede a period of incapacity." In the original that I had written for this section I never meant to indicate that the private mental health care provider could be—would be a surrogate decision maker. I meant that it would be a person who would be more of a monitor of the study, and I just wanted to make sure that would be clear because I think there could easily be some conflict of interest if the provider was appointed as a surrogate decision maker, and I had put in a list of the kinds of private providers that might be there—social worker, psychiatric nurse practitioner, psychiatrist, case manager, etc., but it was perceived as being a monitor, not as a surrogate decision maker.

DR. SHAPIRO: Jim, am I correct that this section you're asking us to deal with right now deals with the issue of fluctuating capacity....

DR. CHILDRESS: Or anticipated....

DR. SHAPIRO: Or anticipated. And, what the surrogate—what this deals with here is setting up a mechanism so that the surrogate could make a decision for the patient in order to prevent harm to the patient which he or she sees developing. That's the purpose here—am I correct?

MS. BACKLAR: It is absolutely correct, and I think the model to use is, for instance, that UCLA study where a patient comes in and agrees to participate in the research has capacity to agree but has a disease that may cause a psychotic episode, and so that these protections are put into place because this may occur, and should this occur, then somebody would be there to make sure that harm did not befall him.

DR. SHAPIRO: It's the last part that I'm most—that's only one phrase in those two pages but it's central to what we're doing here if I understand it correctly. It's that the surrogate's role is to prevent harm to the best of their ability to the patient who has lost capacity permanently or temporarily as the case may be.

MS. BACKLAR: Correct.

DR. SHAPIRO: Thank you. Eric?

DR. CASSELL: I want to agree with Trish that the subject's private mental health care provider should not be somebody who can act as a surrogate permission giver. It's a conflict of interest. I think—I can think of too many times when that person will be from the same institution as the investigators.

DR. SHAPIRO: I think that's right. I think that's a good point.

MS. BACKLAR: Oh, I also would like to say that on page 132 you will see, "but may overrule her instructions to continue participation under certain conditions." Now, those conditions would have to be spelled out, and actually I have them somewhere but I have to find them and I can give them to you in a few minutes.

DR. LO: I have a general comment on pages 131 and 132. As I read it, it seems to envisage a situation where I'm enrolled in a study but I anticipate that my decision-making capacity will fluctuate or decline and so I want to appoint a surrogate to protect me when that happens. Did we not also earlier talk about having a surrogate appointed to consent to future studies where, in a situation that I may lose decision-making capacity but be able to enroll in the study—when I relapse for example—and is that really dealt with here or do we want to say we're not going to do that?

MS. BACKLAR: As far as I am concerned I think that one can only give consent for a study that one knows about. I'm very uncomfortable, and people may not agree with me about giving consent to a future unknown study.

DR. LO: No, no—you're not giving consent. You're appointing a surrogate to give consent for you. A surrogate decision maker, which would, for

instance, be the only way you could enroll someone in a relapse study, for example, where you want to study someone at the time of relapse where they have clearly lost decision-making capacity. I thought before that one of the proposals made was to appoint the surrogate who could step in for you at that time and say acting in those patients' best interest I want to enroll them in the study.

MS. BACKLAR: Well, I have a great deal of difficulty still, I have to say, in agreeing to appoint somebody to—who could enroll me in something about which I do not know anything about unless it's very clear what that study is going to be, and if it is specifically something that you would, as you just described, a relapse study waiting for a time that I should—I might relapse—that might be okay. But one would hope, of course, that one took one's medication and that one did not relapse.

DR. SHAPIRO: Eric, Alta, then Bette.

DR. CASSELL: Trish, how about....

MS. BACKLAR: Decompensate, actually.

DR. CASSELL: How about the person who has early dementia who can still give consent but now their dementia is deepening and along comes a drug study, which has some minimal risk but offers some potential benefit but they no longer have the capacity to give consent. Don't you think that their surrogates, appointed in advance, ought to be able to enroll them in that study?

MS. BACKLAR: Well, I think if Gregg Saks' work and if I was going to be in a study where Gregg Saks was the PI, I'd say yes. I'm concerned about the kinds of protection one would have to have additionally in place if you were going to agree to be involved in a study when you had lost your capacity for decision making, and if you had a surrogate and you have this private mental health provider who would be a monitor, it might be all right.

DR. SHAPIRO: Alta.

MS. CHARO: I think we might be helped here by taking some guidance from the analogous phenomenon in the clinical settings where people ordinarily make decisions for themselves; if they are temporarily or permanently incapacitated decisions are made for them by their legally authorized representatives, something that's usually set up by State law—parent, spouse, various close relatives, etc. But, a competent person is free to say that he or she would like somebody other than the default legal representative to be making health care decisions and they're free to write out a health

care form that designates somebody else. For example, I designated my sister-in-law to make decisions for me in case I'm incapacitated, rather than having it fall to some other particular member of my family. Now, that person is constrained just by the usual rules—they can't make decisions that are grossly ridiculous. The analogous situation here would be that decisions about enrolling people into permissible categories of research—for example, non-minimal-risk research that presents some potential benefit to that subject—those kinds of situations permit enrollment by the legally authorized representative unless there has been named in a document a research representative, the analog to the health care representative. If you happen to have somebody designated like I do, you might designate the same person for both roles; you might have different people. But it's narrowly construed. So, if I say I want my sister-in-law to be my representative for one particular research protocol, and then two years down the road I'm incapacitated, a new research protocol arises. That initial document is not going to authorize you to do anything in that context. It's narrowly construed and authority would revert back to the usual legal representatives that we've been contemplating here. But I might have written a document that said, "For all research protocols, I would like my sister-in-law to be the one who makes the decision." In which case it doesn't matter that I don't know what the reason for protocol is. She can only enroll me in those things that are within the permissible parameters set down, and all I've done is identify the decision maker. That would be an analogy to how it's done already, and the advantage there is that we've got model documents, we've got model State laws, we've got some degree of public familiarity with the process—limited, but some—and we've already got in place a procedure in hospitals for introducing people to these notions and encouraging them to take advantage of it to name these people.

DR. SHAPIRO: Thank you. A number of people want to talk—let me turn to Bette first.

MS. KRAMER: Alta has really covered the situation that I was going to raise. I was thinking of myself if I were diagnosed with a disease where I was going to have—I would have dementia and it would be, you know, ongoing. I would certainly--where my life was going to lose all quality to me, I would like to know that if you could possibly have some quality to society by my being used as an ongoing research subject for follow-up studies. And I would like to have the opportunity to authorize somebody to make those decisions on my behalf, but that would be covered by what you just raised, is that correct?

MS. CHARO: That's right. The way these things work—you really are giving someone else authority to make the decision for you. You're welcome to give them guidance; in fact, you're encouraged both verbally and in writing as to how to make those decisions. Sometimes problems arise where you've written down your

guidance and their decision appears to be somewhat in conflict. I give my sister-in-law guidance that says I want be offed as soon as there's a less than 50 percent probability I'm going to regain cognitive function—and she doesn't do it, right—she keeps me hanging in there when the probabilities are lower. That's in an institute—in a clinical setting, that's where hospital ethics committees tend to get involved in trying to resolve these. But as I understand it, those verbal instructions are not binding upon her. The nature of this arrangement is I have truly delegated the authority. If I wanted to try to control the actual outcomes in specific situations, you would write what's commonly known as a living will, and that's where here in the earlier months we've discussed how difficult, in fact impossible, it would be to do something like that in these settings. So, really, it's a delegation of authority or nothing in these situations, accompanied by persuasive guidance to that representative.

DR. SHAPIRO: Bernie?

DR. LO: Just to follow up on Alta's nice discussion. I mean, these kinds of advance directives serve a couple of purposes. One clears if you have a preference for who should make the decisions as opposed to the natural default. The second is to be able to have some control over future situations you can anticipate. I mean, the nature—you know, certainly in the clinical realm but also the research realm, you can't anticipate all the things that might happen so you can't say, "I'll consent to this study in advance," because maybe the protocol's not designed yet—the drug isn't available. And, in order to have some control you say, well, if I can't control *what's* going to happen, at least I can control *who's* making that decision and I'll appoint someone whom I trust to make the decision as best they can that I would have wanted to make had I miraculously been able to speak on my behalf. The other point I think is the formality of signing a advance directive that's notarized or witnessed or whatever is thought to convey some extra sort of moral force because it's not just kind of an informal arrangement or offhand comment, but I really thought about it. And I think the importance here, and certainly some States clinically made that very important, there are things you can't do without a formal sort of document or very clear oral directive, but here it seems to me that if I really cared about research and I said, you know, I can't anticipate what's going to happen in five years or ten years, but I really—as Bette would say—I really want to be part of research to help other people. This gives you a way to do that and the fact I've gone to the trouble of drawing up the document, going through the formalities make the researcher and the IRB more comfortable that I really meant it as best I could—anticipating the future and that I trusted someone enough to be able to stand on my behalf. So I just think that we're undercutting sort of a desire to participate in future studies that we can't give specific consent to because we don't know what they are. And, you know, although previous things I've said—this is not a panacea. Not very many people are going to do this. But to the extent that some people do want to do it, it

seems to me we should encourage it and permit it and allow the researchers in IRB to use this kind of advance planning as something more than just my family member who's legally authorized on the spur of the moment saying, "No, I don't know what Bernie wanted to do—I suppose it would be all right." That to me has less moral force than "Bernie really wanted this—to participate in research. He signed this document, we talked about it, and as best as I can tell he would have thought this would be okay."

DR. SHAPIRO: Trish, then Alex.

MS. BACKLAR: I want to allude to a number of documents, articles written by Rebecca Dresser, whose point about this I feel very concerned, and that is it's very hard to know what in one mental state what I *really* may want when I'm in another mental state. I'm very concerned about people agreeing to be in a research protocol as much as they may wish and think this is what they want to do with their lives when they no longer have the capacity to make these decisions. It may be a very miserable time for them. And I'm very worried about having people—that was not the kind of anticipatory planning that I meant in this particular situation.

DR. LO: You're not consenting to a specific protocol; you're consenting to let a surrogate whom you choose make that decision, and that's—I mean, we do that clinically all the time. The real question is are you going to have no way of allowing patients to do that for research in advance.

DR. CASSELL: Health care proxy for research.

DR. SHAPIRO: Excuse me. Almost finished, Trish?

MS. BACKLAR: Well, I just want to make it quite clear that this is something that I would be very concerned about are--about my agreeing to in this document.

DR. SHAPIRO: Alex, then Alta.

MR. CAPRON: I think at this point I am in agreement with Bernie's point, and I think that the concern that Trish raises supports that conclusion. The appointment of a surrogate is equally inappropriate because in the situation in which you are in effect saying that the patient in that future state is really not the same person, then why should the present person's designation of the sister-in-law, the case that Alta mentioned, have any greater weight than the usual presumption that it's actually the mother or the father or the spouse or whoever steps into that role. And, I thought in our last meeting that we had, a good deal of discussion of this. And, the—the position that I

took then, which was in line with what Bernie said, was I believe if we're talking about saying that for certain categories of research in particular, there's a presumption against using subjects who are not contemporaneously consenting, that in differentiating the population that you might be able to use from the population you shouldn't use, a reasonable way of differentiating is close to what Bette described, which is those people who say, "I recognize that research involves risks and I'm really not very willing to run risks in a situation where I think I'd likely be very vulnerable and depersonalized in people's eyes," versus those who say "I recognize that research involves risks. If I'm in that situation, however, I would want to be able to have someone consent on my behalf to being in the research." And I think that kind of gross divide—now, whether one takes further steps and say, "I would be willing to participate in research of no benefit to me at all; I'd be research that involves physical invasions"—doing a brain biopsy or something or, you know, some other fairly invasive procedure. I mean, it does seem to me that people have different levels of the sense of being willing to undergo certain risks and—and being used for the benefit of others when they are not consenting and that if we had a method where we thought that people were really being faced with a choice, and at least at this moment were making an intelligent choice, the fact that that might not be the same "person" as that later person still says to me, if we're going to look at all of what I believe today, it makes sense to allow a division, particularly if the result of the division is the people who don't opt through advance directive, to say "I *will* be in nonbeneficial research, and it's okay for my surrogate to consent to non-beneficial research." They will—those people will be protected, and their surrogate can't involve them. To me this is a way of sort of separating out on than basis—and I think it makes sense, and as Alta said, I think it's very close to what we allow with the so-called living will. Maybe—you were saying there is no equivalent; I think there *is* an equivalent. Right now a person can say, "If I'm ever in that situation I want food and fluids or I don't want food and fluids." And in some States if they *don't* say it's okay to withdraw them you must continue them.

DR. CHILDRESS: Would you, Alex—would you have the right to dissent though?

MS. CAPRON: That language is in these pages, and it's very clear that that person may withdraw, but whatever he wishes—whether he/she has decision-making capacity or not, he or she may withdraw from the study—page 132. Absolutely essential. The contemporaneous person can always say, "I don't care what anybody else said," you know. As long you have that—you little green dragon, stay away from me.

MS. BACKLAR: But also that they would have a monitor?

MR. CAPRON: Yes.

MS. BACKLAR: So you would keep in those provisions all those other protections.

MR. CAPRON: But I think a person like Bette who says, "I'm willing—when I have Alzheimer's and I can't make decisions, I'm willing to be in research. I know good will come from the research overall. I trust my husband to decide whether any particular study's all right. My doctor will be there to make sure that the researchers aren't abusing me." And then her next door neighbor who says, "No way. I just know what they do to people with Alzheimer's. They just use them as guinea pigs. You're not going to use me like that. I won't consent." Those two people should be treated differently.

MS. BACKLAR: All right, then, on that page where I had put "under certain conditions," I had written that thinking of certain conditions with people with schizophrenia. And they might be very different. Those certain conditions where your surrogate could pull you out of the study. I think one would have to specify the kinds of conditions where some—the person may be assenting but the surrogate would say no because of harm to the subject. And in terms of a person with schizophrenia, that they had clearly lost capacity for decision making due to a psychotic episode and are at risk of harm due to some aspect of the study itself, but continues to insist that they wish to remain in the study. So, there would have to be.... I'm talking about some kinds of conditions in which the surrogate could say no. I don't think it's right for this person to continue to be in this study.

MR. CAPRON: And the surrogate is still the official decision maker.

MS. BACKLAR: Yes. You have to keep....

MR. CAPRON: Well, if the official decision maker withdraws consent—you know, I mean, the private doctor says to the decision maker, "You should be worried now, and this is getting dicey; this isn't the way we hoped it would go," I would withdraw consent.

MS. BACKLAR: I want to make sure that that's tied on an ongoing basis. The other thing is that it's not made clear here that if it was a study, that the surrogate decision maker—and I said this before, and Dukoff and Sunderlund had written about it—participate in the informed consent process. Now if it's a study that's not immediate, obviously the surrogate decision maker has to be the person who is involved in that information situation. But if it was somebody with schizophrenia, I still would think that during the informed consent process that the person they have appointed should go through that. So the appointment must occur before you even get

into the informed consent process. And, I think that has to be made very clear.

DR. SHAPIRO: Alta, then Bernie?

MS. CHARO: I'd like a clarification about the applicability of this section. If I am somebody who has executed a document appointing Bette to be my research representative, and I have explained to Bette that I am willing to participate in greater-than-minimal risk research that has no potential benefit to me personally. But I'd like my life to stand for something. I want research to go forward. And on that basis I was enrolled, the research went forward, Bette stood there to protect me in case a moment arose when she thought I ought to be withdrawn. Several months down the road a new research protocol is proposed. I am incapacitated at that time, have no knowledge or comprehension that the new research protocol is being proposed. It is another greater-than-minimal risk low-direct-benefit protocol. Can Bette—if I've anticipated this kind of thing—can Bette enroll me in this or is that prohibited to her?

MR. CAPRON: It depends on—I thought you, yourself, answered that before. You said it depended upon what kind of instrument you use.

MS. CHARO: Well, that's where I got confused in our discussion—whether or not the purpose of these representatives is solely to provide follow-up in case I lose capacity once entering, or whether it really is going to be for enrolling in ....

MR. CAPRON: Either or both.

MS. CHARO: Fine. I just—it was clarification, because I suddenly felt at sea.

DR. SHAPIRO: Well, as we bring this to a close—Eric, did you have a point to make on it?

DR. CASSELL: Well, why can't we use the proxy language? A proxy speaks with my voice and can say no or yes. I mean, if I've assigned a proxy I've assigned a proxy. I don't see why....

MR. CAPRON: But some people, when they're going into surgery, sign a proxy and that proxy....

DR. CHILDRESS: Right. Okay, as we bring this to a close, are there any points you still want to make to tie things together—for example, to go back and think at

all now about the risk categories now that we've talked about all the other kinds of protections. I know we're all pretty tired after the morning. If there's anything people want to add, fine; if not, please think about this. Think the specific matters we've talked about. We have a group working on the formulation relative to the limitation criteria, but there may be other things that emerge this morning that we need to get some language on, and anyone who feels that we do, please provide that as quickly as possible so we can get another draft and then really try to sign off on a draft that will then be responded to by others who are able to examine it on the other side.

DR. SHAPIRO: See, can I make a comment—just see if I have misread what was going on before—not the most recent conversation, but back to the risk conversation. My sense is that most Commissioners felt while in any category—a small number of finite categories had some problems with them, that people were much more comfortable with three than with two. And one of—now, that's the sense I have. I just want—cause you're going to need—we're going to have to sort of decide this and work it out.

MR. CAPRON; But I was with you on your observation that it wasn't the number of categories—it's what's *in* them that counts. That's my own view.

MS. CHARO: Could we see a show of hands regarding some gross definition of what "minor" would mean?

DR. CHILDRESS: I missed the first part. Did you want to see a show of hands about...? Okay, how many would—how many think it'll be useful for us to try to work out the set of recommendations in terms of three categories of risk? Do numbers talk, Alta?

DR. CHILDRESS: And those opposed? Prefer two? And those who are skeptical.

MS. BACKLAR: I want to agree with Harold. I think that that's a much more specific way. I don't think the amount of categories is going to count. What is going to count is risk, and how that is evaluated.

DR. CHILDRESS: Right, but his question is how we try to formulate them, then what we put in each.

MS. CHARO: The purpose of having separate categories is to attach different protections to them.

DR. CAPRON: I want to know what's in—if we're putting a column in the middle, I want to see—we have a huge contrast. Under the "minimal" we have any special protections? No.

MS. BACKLAR: But I think that you would need to have some.

MR. CAPRON: Well, we have some in the sense of the IRB is supposed to be different. The determination of whether or not you have capacity is supposed to very precise. That you're not supposed to be in the research at all if there's way of doing it with people who don't have those kind—all of that's true. But as to the special consent requirements or something, we have none.

DR. CHILDRESS: The question is we do say elsewhere in the document that disent will count. Now, is that in addition to the consent requirements that already exist elsewhere? Then if so, we don't need no apparent dissent or no dissent under the greater-than-minimal category. So, it's really a question I'm raising at this point.

MR. CAPRON: Well, I don't think that's true, Jim, because as I said before, I took it that what we were adding to the greater-than-minimal risk is the requirement of consent, but then we were stepping back to the default position of at least no dissent when it's a potential benefit.

DR. CHILDRESS: Okay. That's fine. Right.

DR. SHAPIRO: I know there's a lot more to be said but we can't settle this right now. But it is twelve o'clock and I do want to move to our public comments, so if necessary we'll come back to this. I'm sorry to have to cut off discussion, but we haven't resolved this issue fully yet. But I do want to move on to public comments. So let me do that right now. Eric, you have a list of.... Let me just say with respect to public comments, remind all those who will be participating that the Committee's rules in this respect are five minutes—no more than five minutes—and ask everyone to respect that so everyone else can get an appropriate share of the time that we have available. I'd ask anyone making public comments to please come to the microphone right at the end of this table so that we can hear you easily. The first public comment—I don't know if Dr. Hopper is here, or Dr. Ablin from the Univesity of California—just come up and indicate which one you are and make your presentation.

MR. CAPRON: We have a written submission here.

DR. SHAPIRO: We do have a written submission in this case, yes.

DR. HOPPER: Thank you very much, Mr. Chairman. My name is Con Hopper. I'm Vice President of Health Affairs with the University of California system. I am here today with Dr. Art Ablin, who is the Emeritus Professor of Pediatrics and current chair of one of two human subjects committees at the University of California, San Francisco campus. We appreciate the opportunity to join with you today to share the University's observations as they relate specifically to an issue that's not before you today, but it's a proposal before the Commission regarding the structural relocation and functional expansion of OPRR. As mentioned, you have a copy of our testimony, and I—certainly in the interest of your stomachs and time—won't try to repeat this in detail. But by way of background, the University of California is the designated research university for the State of California, and we have a mission with a major emphasis on research and a historical commitment to the advancement of science and technology. We operate nine campuses and, under the federal government, three national laboratories. We collectively offer, we believe, the largest program of health scientists in the nation. And obviously the scope of activity involving human subjects research is substantial, with more than 10,000 protocols reviewed annually by the UC medical school campuses alone.

The University appreciates the complexity of the issues facing the Commission and the University takes very seriously its responsibility for ensuring the protection of human subjects in a manner consistent with federal guidelines and high professional and ethical standards. We believe that good science, carefully reviewed and closely supervised through the nation's existing system of decentralized Institutional Review Boards, is a strong and effective mechanism for advancing the parallel goals of quality science and human research subject to protection. In this regard, we believe that many aspects of the current system are working quite well; however, at a system level the University of California also recognizes the need to continuously monitor our efforts related to human subjects research and to make improvements as needed. And in this regard, several months ago the President of the University of California appointed a clinical policy review team and assigned it to examine current practices in existing oversight mechanisms as they relate to quality assurance, medical staff credentialing and privileging, risk management, and—very importantly—human subjects research. To date, four of our five medical school campuses have been reviewed, and the fifth campus review started recently and is scheduled for completion later this year.

With regard to human subjects research he team shared three, major observations. First, we believe that our committees are comprised of dedicated faculty who are committed to providing thorough review of research protocols and to ensuring to the fullest extent possible compliance. Secondly—and this is very important—our committees are subject to extremely heavy workloads and work hard to conduct their business with efficiency and objectivity, and although some issues related to workload

have been improved through the formation of additional campus committees, a lot remains to be done in this area. And finally, new resources to support educational efforts within the campus research community are desired by most human subjects committees and chairs. And we are committed to trying to arrange that. It's anticipated that upon completion of this review, a series of system-wide recommendations as to best practices will be created and shared throughout the university.

I'd like now to turn to Dr. Art Ablin, someone who has had up-close and personal experience with these matters, both as a clinical researcher and now as chair of an IRB at UC San Francisco. Art.

DR. ABLIN: I'm a pediatric oncologist with over 30 years of experience at UCSF, with well over a hundred human research protocols having been approved by our IRB. And presently I am the regulator—I am the chairman of the IRB. I'd like to share with you three areas. First, my perceptions as both a clinical researcher and now chair of an IRB. Secondly, I'd like to talk about what I think are unevenness in the quality of human research and the oversight of that research. And thirdly, I'd like to address very briefly the perceived area of conflict of interest between the OPRR and the NIH.

First, my perceptions as a clinical researcher and as a chair of an IRB. I think the system's working very well for us at the University. We are a dedicated group of peer reviewers who have the interests and protection of our human volunteer very high in our minds. We are relentless; we're diligent; and we're strict. We are very concerned about the protection of our human volunteers. We are also aware and our peer research mechanism works well to ensure that we continue our research efforts at the University. And that allows us, I think, to have outstanding human research. We feel—we're very aware of the oversight that we have of our IRB at the office of the Vice Chancellor of Research. We're very aware of the office of the President of Research Affairs. And we're certainly very aware, cognizant, and appreciative of the oversight that we get from the OPRR. We recognize we can do better. We continually try to do better. We're not perfect. What would help us most of all would be to have increased resources and increased funds for the education of the researchers at our institution about the existing regulations and about bioethics. We really need help in that area.

Now, the second area I'd like to address is what I perceive as an unevenness in the quality of human research and in the qualify and intensity of the oversight of that research. And that exists in the non-university private area, or the possibility exists in the non-university private area. I think it would be wise if the regulations for that area—if the resources to regulate it—were improved and increased. And I think with that we would see an improved quality of human research, and with

better oversight. Our human volunteers deserve the highest and best care, no matter where that research is conducted—whether it's conducted at a university campus or in the private area.

The third area I want to address is this perceived conflict of interest in the position of the OPRR and the NIH. I think that there is a possibility for that conflict of interest. However, I don't think it should be fixed by establishing a new agency and increasing the bureaucracy. I don't think we need more bureaucracy to fix that. How exactly, I don't know. Whether the person who has the budget oversight should be changed. Whether the OPRR should be moved to another existing agency. Those are all possibilities, but certainly not establishing a whole new bureaucratic control. And I'd like to now turn the microphone back to Vice President Hopper for concluding our remarks.

MR. HOPPER: And given the time, these will be very brief concluding remarks. We essentially believe that what we're doing in the State of California actually works. We believe that the communications at the federal level can be improved. You will have to decide how that happens, but we think we'd like to keep on as we are at this point in time. Thank you.

DR. SHAPIRO: Thank you both very much, and thank you very much for coming here and taking the time to share your thoughts with us. And thank you also for the written submission we all received. Any questions from members of the...? Yes.

DR. COX: I have a question for Dr. Ablin. Maybe I misunderstood. I certainly appreciate your point about education of the scientists. But is it—did I understand you correctly that the rate-limiting step in such education are resources and extra resources to be able to educate them?

DR. ABLIN: Yes. You did understand me well, David. We need money. We need people at our institution. We need an educator. And if we could educate our researchers—our researchers don't have to be motivated to protect human subjects; they just have to know how to do it. They want to do it, and they just have to know how. We spend endless hours at the IRB going over and over consent forms.

DR. SHAPIRO: David, quickly.

DR. COX: One quick follow-up to that. So, that, you see this education being sort of divorced from the other—not divorced but separate from ongoing education in other types of courses that the scientists and students would get as opposed to being integrated into the other things that they're doing.

DR. ABLIN: I think it's both. I personally would like to see a requirement to submit a research protocol with a consent form to our IRB that the researcher has to have attended a course on human bioethics, a course on the regulations and the proper writing of an informed consent.

DR. SHAPIRO: Thank you. Diane has a quick question?

DR. SCOTT-JONES: Yes. I just have a question about that same question that David asked. I understand that your current researchers are probably not your former students, but are your students now getting the kind of instruction in their courses that would satisfy what you're in fact recommending?

DR. ABLIN: I'm not sure that I know how to answer you question. Bernie can. They get some instruction. But when it comes right down to the nitty-gritty of having a research project and having to write an informed consent form, that's what we're finding difficult.

DR. SHAPIRO: Bernie, do you want to make a comment?

DR. LO: I wanted to say publicly some things I said during the break. Dr. Hopper mentioned a study, a clinical policy review team which looks at human subjects needs. I really encouraged him, and I think for other members of the Commission, if possible to make available that report, particularly the—we appreciate the conclusions, but the—the findings, the data from which those conclusions were drawn because we really don't have a lot of solid, empirical information as to really what's going on out there at the institutional IRB level. And I think that would be helpful not just for us but for the public dialog.

DR. SHAPIRO: Thank you very much. If that's possible, we would appreciate that. Thank you. The next person to address the Commission is Ms. Kathy Kasten, who wants to talk to us about human subjects. Ms. Kasten.

MS. KASTEN: Thank you for the opportunity of allowing me to do this presentation. To preface my comments I want to say this: I do understand that the FDA, NIH, OPRR is part of DHHS, okay? I would like to cite from 21 CFR part 50, document no. 90N-0302 *federal Register* 10/23/97, pg. 3. After presenting the DoD's explanation as to why obtaining informed consent was not feasible, the report states that the FDA gave considerable deference to the DoD's judgment and expertise regarding the feasibility of obtaining informed consent under battlefield conditions." I noted that none of the DoD's reasons for waiving informed consent involved questions as to the risk factors to human subjects of the combination of drugs to be utilized. In fact, the DoD

was not concerned with a preventive or therapeutic treatment that might save a soldier's life. Isn't one of the charges of the FDA NIH to at least involve itself in the public good; i.e., to make sure at least the drugs administered to the American public have therapeutic value? This is not the first that the FDA/NIH has deferred public responsibility to other agencies, researchers, professional health care personnel, or drug company executives. I unwittingly, covertly, was involved in an experiment which was funded, I was told, by the NIH. My ex-husband was a co-investigator in an experiment involving radiation of microwaves directed at a pregnant woman. The woman was to stand directly in front of the microwave source. I can testify to the facts of that experiment. I can testify that I was coerced and lied to. Years later while making an appeal to the NIH to stop covert research, I requested the file on this microwave protocol. I had the date of the experimental period, the place where it took place, and the personnel involved. I was told that studies funded by the NIH/FDA were not kept on file. No paperwork of outcome was filed with the NIH/FDA. Am I now to infer that the FDA/NIH deferred to who—the principal investigator? The institution who provided the space for the experiment? Is the FDA/NIH by their explanation telling you that they have no responsibility for how the American taxpayer monies are spent and on what type of research? Technology from this type of past experimentation research funded by the NIH is now being utilized against American citizens. Technology that the American citizens paid for through taxes on their wages for productive work is being utilized against them. Who is responsible for funding projects that are now utilized against innocent American citizens? The NIH/FDA. I wonder why this is so. Is it because there's been a policy of cross-hiring of personnel from other agencies who have a vested interest in covert research? Is it because ex-drug company executives are cross-hired by the NIH FDA? Is it because of the old ties that this has happened? Perhaps the American people should consider abolishing this agency because of its record of deference in favor of a Cabinet-level position, a Cabinet office which would seriously serve all of the American people, not just vested interest, which would be involved in all protocols, whether the research is performed by private industry, public agencies, or academic institutions. And yes, I understand the office is only as good as the occupant of that office. Therefore, I would further suggest two absolute policies: (1) public access and review of that office through a Congressional committee and/or a citizens committee; and (2) severe monetary and criminal penalties for researchers, company executives, and academic administrators who violate human subject protection rights guidelines. Thank you.

DR. SHAPIRO: Thank you very much. If you'd like to share the document with us, we would have reproduced for each member of the Commission, but that's up to you. Any questions from member of the Commission. Thank you. Next person to address us is Ms. Maxine Haden, San Ysidro, California. Is Ms. Haden here? I don't see—the answer to that is....

MS. NORRIS. She has not signed in...

DR. SHAPIRO: Ms. Betsy Manning?

MS. MANNING: Thank you. The title of my five-minute talk is The Use of Electromagnetic and Neurological Weapons Against Non-Consensual U.S. Citizens. Imagine a radiation victim asking your panel for help and you have no knowledge of the classified atomic bomb research. My task is strikingly different. I pray that the results today will be different than the results of ignored complaints of the radiation victims 40 years ago. I come before you today on behalf of over 1,000 U.S. human research subjects targeted by the above-classified research. The National Bioethics Advisory Commission charter states as its first priority protection of the rights and welfare of human research subjects. On January the 22nd 1997 Bill S193 was introduced in the Senate by John Glenn, titled Human Research Subject Protections Act of 1997. To this date—February 6, 1998–this bill has never been passed. Who's being targeted by these types of weapons? Whistle blowers, prisoners, alternative health practitioners, dissidents, and anyone else in charge—any one else those in charge decide to target. How are these groups being targeted? Through electromagnetic and neurologic weapons programs by satellites and other weapons developed by the intelligence communities to the control the mind. Why are CAHRA—that's Citizens Against Human Rights Abuse—and similar groups not getting in help because these types of weapons remain highly classified. Secrecy. According to the Commission on Protecting and Reducing Government Secrets, Daniel Patrick Moynahan, New York, Chairperson, states in summary, "Secrets in the federal government are whatever anyone with a stamp decides to stamp secret." Classified and declassification have been governed for nearly five decades by a series of Executive Orders. The National Security Act was used to cover up radiation experiments, and now electromagnetic technology experimentation. Examples of help being refused to victims: The *City Sun* newspaper December 21st, 1993, "Implant Victim Refused Help by Humanitarian Physicians." The Boston chapter of Physician for Human Rights refused to examine or treat government implant victim Brian Rong against the protest of some of its members. Rong was found positive for paramagnetic metallic foreign bodies in his head and chest in 1991. No surgeon would remove the implants, citing FBI retaliation. Example 2: about a year ago CAHRA contacted an MD with Physicians for Social Responsibility and asked her to review the medical records of these victims. The physician agreed. About the three weeks later the doctor withdrew, stating she didn't want to put her family at risk. International Red Cross. Robert Copeland, employed by the International Red Cross, Geneva, Switzerland, wrote an article for the *British Medical Journal* in 1997, July 12, titled "Nonlethal Weapons Precipitating a New Arms Race." Will the soldiers who have survived battlefields of the future return home with psychoses, epilepsy, and blindness inflicted by weapons designed to do exactly that? He said, "Should not these questions be considered before such weapons are deployed?"

And my question, now, to you, the panel, why are victims complaints that the government is experimenting on their minds so far-fetched when the government has these types of technologies to create psychosis as a military weapon? Victims' efforts have failed to stop this atrocity just as the radiation victims failed four years ago. Many of these victims are having their lives destroyed due to the secret electromagnetic technology. Citizens need to decide for themselves if this technology exists after being presented the facts. Is it not time for a Congressional hearing. CAHRA is a nonprofit organization who works tirelessly to open up this highly classified research of electromagnetic and neurological weapons experimentation on human subjects. CAHRA can be reached through her Web site listed below, and I'll leave the paper. Thank you very much.

DR. SHAPIRO: Thank you very much for being here today. Is there any questions from any member of the Commission? Thank you. The next person to present is Ms. Joan Siegemund, if I've pronounced it correctly.

MS. SIEGEMUND: Yes, that's correct. This is not supposed to be a show-and-tell; however....

DR. SHAPIRO: Would you step up to the microphone? Perhaps we could lower it to make it a little more comfortable for you.

MS. SIEGEMUND: Thank you. Yes, this is not supposed to be a show-and-tell session; however, as luck or whatever would have it I have something to show. This is the rash and the blister that many of us covert, non-consensual electromagnetic targets, subjects have had over the years. Mine started about seven years after I contested an illicit guardianship matter, a very severe, severe violation of all the guardianship regulations in Massachusetts and Maine, and brought the matter to Supreme Judicial Court of Maine. The person that I was trying to protect was my mother, who was being drugged with Haldol, and the apparent attempt was made to simply end her life and to use whatever information they had weaned from these experiments and to simply finish off the embarrassing matter. I wasn't obviously meant to discover what was going on, but how can you not persist when it's your own family? I found out too much and then things started happening. Not only robberies and vandalism, but then about a year and a half ago this all started. Now, I'm wondering what can be done by this wonderful group assembled here because as I see it, the matter is much more vast than can be handled by any legislation. It's been said that you cannot legislate decency. You cannot legislate conscience. You cannot legislate a feeling for humanity. As much as I laud your attempts, your good intentions, I feel that the problem will have to somehow encompass all the agencies—covert—and not quite as covert who somehow managed to not disclose their budgets or what the budgets are used for. I

agree with the doctor here that there is a distinct need for education. I know that in Europe, for example, people are totally amazed at the widespreadness of this type of thing. Of course, these electromagnetic weapons are available worldwide. I have a document that is offering a kit for fifteen dollars to make them up yourself to use on whoever you wish to for amusement purposes, punishment, whatever. The education, I think, is the most important thing. You cannot legislate. education. It will have to be something much, much more profound and I wish I could help you out in this—I have no answers. But I have discovered that all the wonderful doctors I have gone to who have tried to help as much as possible and have indeed helped. I do know that some of them have not been unwilling to give the results of all of this to a certain covert agency. That I can attest to for sure. They have not said so in so many words, but there is no doubt about it. And they have somehow managed to alleviate the impact of this because last—just about a year ago I was diagnosed with leukemia, which I attribute to electromagnetic radiation that was extremely intense for four months. No let-up—night and day. No one in our family has ever any kind of leukemia—any cancer.

DR. SHAPIRO: I apologize for interrupting but are your remarks nearly through?

MS. SIEGEMUND: Yes, I am, sir. Yes, yes. I would like to impress on this Commission that you cannot legislate anything decent. You have got to go to the top and allow the press, for example. Impress the media with the vast importance of disclosing this rather than keeping the lid on. I thank you very much for your attention.

DR. SHAPIRO: Thank *you* very much. Any questions from members of the Commission? If not, the next person who wishes to address us is Ms. Felicia McCarty, Miraloma, California.

MS. MCCARTY: Thank you. Does this go up?

DR. SHAPIRO: I think it goes up and down. Pat, can you help out?

MS. MCCARTY: Thank you. I'd like to thank Ms. Norris for allowing me to speak today. The fact is that I wasn't signed up because I didn't think I'd make it here. I had a car breakdown and various other physical difficulties to cope with right now, but I was able to get here and I'm glad that I did come because I do have some things to say. My report went into NBAC with regard to my son, a forensic patient, who is one of the most vulnerable populations in California and probably in the entire Union, because they don't have any say about what research is done on them. I became aware of this through a peer advocate—by the way, I have been with an organization called Support Coalition International, which defends human rights in psychiatry and promotes

alternatives. My son was adjudicated in a court of law for what I would consider a minor crime--property damage and one count of theft 20 years ago. He has been incarcerated for over—for 21 years, over 20 years. In recent times I began to delve into human subject research and I have a peer advocate friend to thank for that. I began to demand accountability from the facility, namely Patton State Hospital in Sacramento—over in San Bernardino, California, after which he was immediately transferred to Metropolitan State Hospital, which by the way, has made the headlines. And this is not show-and-tell, but I wish to bring to your attention that the *L.A. Times* has done a number of articles on abuses of mental health clients in California, including the jails. The Los Angeles jail—and I can attest that all of the jail psych wards are as rotten. The Justice Department did an investigation, and that, too, was a major issue in our *L.A. Times*. I'm wondering why the *L.A. Times* isn't here because the *L.A. Times* has been hitting on these issues quite frequently of late, and I would suggest wherever this Commission goes in the future that press releases be sent out to major newspapers. I was told by a peer advocate who began to make queries into NBAC about research why this is not general public knowledge, and the response is, "We don't get inquiries." Well, you can't get inquiries—powerful inquiries—if the public, who pays the bills, doesn't know you exist. Is that right? I'm sorry, I don't mean to be abrasive but I'm a parent who has suffered through this, and then becoming aware of human subject research being done on my own son under the guise of clinical trials for which I now have proof and information of which is now in the office of the Justice Department—Human Rights Litigation Department. I have functioned—I'm 65 years old, by the way—I should be out fishing, enjoying myself. Instead, I elected—even during my full-time working years as of 13 years ago—to become an advocate—an avid, adamant advocate for the rights of mental health clients throughout this Nation because their rights have been abused, violated all down through the history of the mental health system. That is, I functioned without pay as a volunteer. Okay—I wrote a rather lengthy report here and I'm told I must stay down to five minutes so I intend to do that...

DR. SHAPIRO: We would be glad to receive it.

MS. MCCARTY: ...and to—and speak so that you can—I don't wish to have rapid speech here—I might be diagnosed as bipolar or schizophrenic—that really doesn't matter to me. They are labels. But what I know to be true—I'm deviating from my report here—maybe I should—just ad lib—I have noted that labels exist. They come into being for the express purpose of pushing drugs. From the top down. I would like to bring to your attention to my personal interaction with two very distressed parents of a young lady on Clozaril in California. I can't guarantee this as being fact, but my understanding is that six million dollars went down the drain on Clozaril research in California alone. That's my tax money. But not only that, I've been told there's only been one death. That was through a hospital administrator when I inquired. From

Clozaril. Lie. Big lie. Big lie! These persons were very distressed about the deterioration, the condition, the bloating, the ugliness of the Clozaril experimentation that they learned was experimentation that was done on their daughter through the county clinic. They asked me to go with them to a meeting with a psychiatrist—the county psychiatrist—and also the head of the pharmaceutical company in that county. Well, I went. But of course I was booted out because it was only family members. And I wasn't surprised because of confidentiality and I didn't protest. But I sat in a waiting room outside that conference room and I heard that county psychiatrist coercing and threatening those parents that if they in any way interfered with their daughter's treatment he would take them to court and remove their partial conservatorship for which they had worked very, very hard in their middle class condition and a father who had been damaged in a recent automobile accident as if they weren't having enough trauma to begin with. Cajoling and coercing them like, "I am authority and you will do as I say." It made me very angry because I knew that's kind of Nazism that exists in that system.

DR. SHAPIRO: Ms. McCarty, I'm very sorry to interrupt you, but would you bring your remarks to a close, please?

MS. MCCARTY: All right, fine. I have a business card which has the side view of the brain with wings on it, which signifies freedom and the right to choice. The man—the pharmaceutical gentleman—came out into the hallway and I handed it to him. His eyes bugged—indictment, right? What these people do when the spotlight is on them—they run into hiding. Well, they soon shifted her to another community very near to her parents and bent over backwards to get her off of the Clozaril. She's still suffering, however, terrible, terrible iatrogenic effects. The same kind of thing has been done to my son. And I therefore—I therefore j'accuse the mental health department in California of negligence, of vicious, vicious treatment of mental health clients and that includes my own son. My report is in the Justice Department's office at this moment. By the way, the Justice Department has been in California already, and I was just wishing this Commission would have notified the *L.A. Times*—hey, we're here. This is human subject research, folks. It involves the well-being, the very life's breath of human beings. Maybe next time they will be.

Child abuse at Metropolitan State Hospital—that's why institutional and private research must be separated. These people don't have a right to say no. They are coerced in one way or another. Threatened, frightened, tyrannized if they say no. Or—or it's five points maybe. I could draw you some very fine pictures of that.

DR. SHAPIRO: Ms. McCarty, are you about to wind up your remarks.

MS. MCCARTY: I'm saying that I hope that you--that this Commission

really does some work in getting the inputs of the general public of parents like myself who have become—I am a career advocate, by the way, and patients who have been sorely damaged, some for a lifetime, in a system like this. Thank you all very much.

DR. SHAPIRO: Thank you very much. I very much appreciate the effort and if there are any materials you'd further like to share with us, we'd certainly appreciate that very much. The next person to address is Dr. David Shure. Is Dr. Shure here?

Dr. Shure is from the National Institute of Mental Health. He wants to talk about the interim report that we've all been working on.

DR. SHURE: Right. Well, actually I've already given you some written comments on the last two versions of your document and I appreciate your giving us the opportunity to comment on the document. The version we delivered last month was six pages, single spaced; the one we delivered yesterday was down to four pages, single spaced—so, I guess we're moving in the right direction.

I just want to say that NIH has ongoing concerns about protecting human subjects, and the NIH director, Dr. Varmus, convened a group that met December 2nd and 3rd in Rockville to bring together people who have expertise on the kinds of disorders that can impair competence of individuals, and individuals who also have expertise in clinical research methodology. As you can see, we have individuals with expertise ranging from theology to bioethics to advocacy to psychopharmacology, geriatrics, and schizophrenia. I think the other things that these people brought to the table that cannot be overemphasized is that virtually all have served as members of their local Institutional Review Boards for an average of five years. So, they have routinely been considering the kinds of practical issues of balancing risk benefits, alternatives, looking at informed consent documents, etc. We also brought in some experts to discuss a variety of issues, which you can see Dr. Applebaum talked with us about competency. We also heard from people with expertise on disorders of children and the aging, as well as some of the regulatory agencies and advocacy groups. This is a further list of the presenters—again, individuals representing the advocacy community and a variety of experts, including some people who frankly oppose research involving people with severe mental disorders.

I'm going to cut to the chase with my five minutes and give you the draft panel recommendations, some of which will mesh very well with your recommendations; others of which may stand in rather stark contrast. Our first recommendation is that when considering individuals with questionable capacity to consent, the IRB should include at least one voting member with the willingness and capacity to represent such

subjects independent of the research and the investigators and, as appropriate, additional voting members representing the family members, patient advocates, etc., and others not affiliated with the research institution. As you know, the federal regulations specify there must be at least five IRB members, at least one of whom must be from outside your organizations. One of our concerns was that some of the larger IRBs with 20 or 30 members may still only have one outside advocate, and our concern was that unfairly dilutes the impact and the insights of such individuals. So, we are, I'm fairly confident, going to argue that proportional representation be maintained so that the voices outside the institution are heard and taken into account.

Now, our second recommendation is that--well, Gary Ellis made the point that a great many of the things that we would like to see changed are actually things that are already contained within the current federal regulations. IRBs may not be aware of them; IRBs may not be taking advantage of them. And, I think there's a great deal that we can already do within the framework of the regulations. Our general approach has been the usefulness of a sliding scale assessing the levels of risks, the benefits, and their relative capacity to consent in order to guide IRB decisions regarding additional safeguards, monitoring, etc. We believe that family members should be involved; that when we're talking about research with particularly high risk—that's the kind of situation in which independent monitors should be employed rather than doing this automatically across the board, whether it's really appropriate or not. Also, that that the IRB already has authority to make this process visible throughout. The IRB can appoint members who may be family members, who may be independent clinicians to observe the recruitment assessment, informed consent process, etc., and we plan to advise them to take advantage of some of these capacities. They already have. (Don't worry, I only have seven recommendations and there are two on the last slide.)

DR. SHAPIRO: Only have a few minutes left.

DR. SHURE: Okay, good—I've only got a few slides left. Individuals with questionable capacity we believe should have a family member or legally authorized representative service--surrogate, and this role should be documented whenever possible. These decisions should reflect the views of the individual when decisionally capable. I think that should be the case whether the individual wishes not to participate in research,—or, if the individual wishes to participate in research we believe that individuals should have a right to say yes as well as a right to say no. Again, we advocate a sliding scale such that the protections would be increased as the risk of a given protocol increases. Actually, these are taken from our report, which is in the clearance process. As you know, speed in government is a relative term. We have it cleared by NIH; we're working on HHS. I hope by the time of your next meeting in Washington, D.C., we'll be able to distribute the final report. As you already have heard, there are no

ideal instruments for assessing capacity. NIH should prioritize the development and testing of such instruments; furthermore, we believe appreciation is the key standard. And as you heard yesterday, that's the one which is probably least adequately assessed by currently available tests and actually may be better assessed by clinical interviews.

Next to the last--rather than focusing on whether an individual is or is not capable of informed consent, there is actually considerable literature on how to improve the understanding of given individuals of protocols, presenting information repeated over time in small doses in the presence of family members who may serve as valuable translators of such information. Encouraging questions can be very useful; it can also help assess the degree to which the subject really appreciates both the risks and benefits of research and how those apply to that person.

And I think I've found my last transparency, yes. Conflicts of interest. People with mental disorders, substance abuse disorders, or neurological disorders may find it particularly difficult to understand some of the multiple roles that individuals may have, making therapeutic misconceptions problematic. We believe that such potential conflicts of interest need to be formally addressed by the investigators considered by the IRBs. They may need to be written into the consent documents.

And last and perhaps not least—the common rule we believe should apply regardless of who funds research. Thank you. I hope I haven't run over my time.

DR. SHAPIRO: Thank you very much for that report. We look forward to getting the materials. They will certainly be very helpful to us in considering our own recommendations.

MR. CAPRON: Are we permitted to send any word back with Dr. Shure?

DR. SHAPIRO: Are you permitted to what?

MR. CAPRON: Send any word back with him.

DR. SHAPIRO: Yes, you can....

MR. CAPRON: I must say that I would hope that, having not seen your draft, that it acknowledges with thanks the role that advocates from patients have played in provoking this reexamination because it seems to me that the gist of what you're saying is all of these things are really possible already. And yet if we hear from you and from OPRR that IRBs are not doing this and investigators are not doing this and have not been told they had to—it's only on the agenda of everyone because complaints have

been raised and finally the attention is strong enough. And, I hope that we, too, in our report acknowledge the role that patient advocates have played in making this a subject that cannot be ignored.

DR. SHURE: I think that's fair and in fact the reason we held this particular meeting at this particular time was a recommendation by Laurie Flynn of NBAC who met with Dr. Varmus—my boss's boss—and that's why this particular meeting took place at this particular time.

DR. SHAPIRO: Jim, do you have a question?

DR. CHILDRESS: Yes. I wanted to thank very much the NIMH and other co-sponsors of the conference, which was attended by at least five of us. Not only do we appreciate the opportunity to hear this and look forward to receiving the written recommendation, but also we are delighted to hear the discussion and actually to build on some of those recommendations in the report itself. So, that's been a valuable opportunity; we are grateful to you.

DR. SHAPIRO: Thank you. Thank you very much. The last person to address us this morning is Mr. Robert Alter. he addressed us also yesterday, as you may recall. Dr. Alter is here again this morning.

MR. CAPRON: It's Aller.

DR. SHAPIRO: Excuse me. Aller. I apologize.

MR. ALLER: I'll be very brief. I've found, and I think many of us have found a real attention to the wrenching issues that Committee members—Commissioners are working with subjectively and objectively and we can see how serious these issues are being taken and we think that's a very important step forward and probably never done with so much feeling. One interesting point about NIH is meeting—the larger meeting that was just reported was there was no report on compliance or noncompliance. I'm essentially reemphasizing what I was talking about yesterday. And also with the University of California, which I'm a graduate of UCLA, but a very large system—but we don't know yet about compliance or noncompliance with the federal and State regulations, informed consent. And, I think the Commission to release any draft document without first having in front of it some real data that says, "It's not as bad as we thought" or "It's worse than we thought" or whatever. And while you're looking at these 300 protocols and it comes down to a smaller number of protocols and form consents that are gathered and analyzed, I think those documents are instrumental. In the radiation commission work they did do that, and I think they're instrumental for

those who are going to review your draft to see how they respond to it because otherwise it's somewhat in a vacuum and somewhat based on anecdotal information. You had families and you had the universities come and say everything's fine. But there isn't any hard data and the people I've talked to said there has been no systemic—or no systemwide look at informed consent to see whether it's largely deficient or it's largely in compliance. All I know is what I've talked about. We've seen a lot of deficient consents but we don't have hundreds of them and we haven't been able to come to any conclusion, so our feeling is very strongly that the Commission needs the data that's about to arrive or going to be gathered. Certainly it can be produced very quickly. NIMH can very quickly produce all of their informed consents for all of their intramural research, certainly the University of California could provide very quickly any of the extramural research. I think the universities with the commissions efforts would cooperate very quickly. I think that would lend a lot of credibility to whatever report and whatever people are going to evaluate. They have something to go on.

DR. SHAPIRO: Thank you very much. We very much appreciate your comments. Any questions from members of the Commission? In that case, this ends our public comments section. We are running about a half hour on our agenda. It's close to one o'clock now. Let's absolutely assemble by two. Let's take an hour but really no more because that'll already squeeze our afternoon. Thank you very much.