DAY TWO: OPENING REMARKS

DR. SHAPIRO: I apologize for our late start because we have been trying to accumulate appropriate materials for our discussion this morning in a way that would enable it to proceed in some kind of orderly fashion. We have a number of things this morning that I'd like to touch base on before continuing. First of all, some of you may have noticed earlier this morning, Henrietta's with us and was, at least, sitting in the back. Henrietta, are you there?

MS. HENRIETTA D. HYATT KNORR: Yes.

DR. SHAPIRO: Yes. I really want to thank you very much for all the work you've done for NBAC, and we'll try to record in our minutes our great appreciation for all that you've done for us. So thank you very much, and thank you for being here today.

PRESIDENT CLINTON'S REQUEST RE: EMBRYONIC STEM CELLS

DR. SHAPIRO: Turning to our business this morning, I think we should allow an opportunity with respect to responding to the President's letter. We take on a set of issues where some of us may have conflicts regarding possible future regulations or other public policy issues involved. And so I think it's healthy for us to just go around the table and if we do feel that there are any conflicts that any of us may have in this area, we should simply put them on the table and we'll proceed from there. I don't think there's any significant problem, judging by the comments that were made yesterday. So now let's just go around the table and see what conflicts you may have. Bernie, you want to start?

DR. LO: I don't have any direct conflicts. (Unintelligible)

DR. SHAPIRO: Thank you. Rhetaugh?

DR. DUMAS: I have no conflicts.

DR. SHAPIRO: David?

DR. COX: Harold, I misunderstood your directive in terms of what we're conflicted about.

DR. SHAPIRO: Well, we are going to be giving advice over the next months, and indeed in the letter we might send today to the President, regarding public

policy issues or issues that might affect something we're involved in. And it's a question of whether you think that gives you any conflicts or not.

DR. COX: I hear you. So with respect to this letter, I have no conflict. Except that I can sign it.

DR. SHAPIRO: We'll try to get along with that. Alta?

PROF. CHARO: Thank you. As I mentioned yesterday, I've had some involvement with the experiments at Wisconsin that were done by Jamie Thompson and published in *Science*. I spoke with Jamie before he began this research on the meaning of separating one cell from *any* form of Federal funding in order to make sure that he did not violate the ban. I did not serve on the IRB that reviewed Jamie's work, but I do serve on a university Bioethics Committee that looked at his work after it was completed on behalf of the university and that has made recommendations about licensing restrictions that should apply when his cells are made available to other researchers. And obviously, being at the university, it has economic implications for the University of Wisconsin if Jamie's patent is granted, but that does not affect me personally.

DR. SHAPIRO: Arturo?

DR. BRITO: I have no conflict.

PROF. BACKLAR: As far as I know I have no conflicts.

DR. CHILDRESS: I'm not aware of any conflicts.

DR. SHAPIRO: I don't believe I have any direct conflicts; however, as president of Princeton University, it's quite possible that there are members of the faculty and others who might have some interest in this area and may have some interest in the way public regulation works out in that respect. Tom?

DR. MURRAY: I have no conflicts on this that I'm aware of.

DR. GREIDER: I'm currently at Johns Hopkins University, where some of the work on the human embryonic stem cells was done, reported by John Gearhart in *PNAS*. And although I do not know John Gearhart, again, because I'm at Johns Hopkins University, that would be the only potential conflict.

DR. SHAPIRO: Eric?

DR. CASSELL: I have no conflict.

MS. KRAMER: No conflicts.

DR. SCOTT-JONES: I have no conflicts that I'm aware of.

DR. MIIKE: No conflict.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Less conflicts than you think. I'm a member of an industry organization where members of the industry are performing this kind of work, although my company is not. I'm co-chair of the committee of the industry organization that requested the President to ask NBAC to look into the issue. And in a former life I founded a company that did active work in this area, although I no longer have any interest in that company.

DR. SHAPIRO: Thank you, thank you all very much. Let me indicate what the business is before us. We will adjourn at noon today, or at least no later than noon, which gives us an awful lot to do this morning. I want to spend the bulk of the time on the Human Biological Materials Report, since we might be able to begin thinking about sending that out for public comment. However, we have a couple of issues left over from yesterday. We are currently typing out, or will distribute shortly, the recommendations from our Capacity Report that has been revised as we approved yesterday. As far as I know, there are no changes in that beyond what we approved yesterday, but we'll look at that in a few minutes; there might be some small changes we want to point out to you as we go through those. That will happen shortly. We then, of course, have the letter to the President, which is going through a draft right now, and we'll take a look at that and see where we are in that area. We may or may not be able to get that letter done today in the sense of reaching a satisfactory conclusion. If we do not, I will work on that letter in the next day or so and will communicate by fax as necessary, so we'll just have to see how that goes.

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

DR. SHAPIRO: Let me now turn to the Human Biological Materials Report. We'll interrupt ourselves as other things become available. And let me turn now to Tom to see how we want to—what issues you would like to proceed with first. Tom.

DR. MURRAY: Thank you, Harold. I'd like to begin by putting to rest once and for all the terminology we're going to use about identifiability/unidentifiability, etc. We have been around this particular hill a number of times, and I just (UNINTELLIGIBLE). We should have exhausted any possible nuances, yet we always seem to be finding new ones. The section in which these definitions are given begins on page 57 (UNINTELLIGIBLE). If you want, you can look at Kathi's memo of the 12th of November, where basically Kathi just asks us to decide on these issues—the section of the report she gives on page 57. The central material begins really on 58, and continues on through with some very good examples, I believe, to about 65. Now, I don't want to

do line-by-line editing; I want to know if we are comfortable with the concepts, the definitions, and the examples.

DR. GREIDER: The definitions as given in the section that you're talking about I don't have big problems with. But when we get to the recommendations section the wording is different. And therein lies my problem. I can delineate exactly what that problem is if you would ....

DR. SHAPIRO: Why don't you give us an example?

DR. GREIDER: I think that the most straightforward way to define these samples is to first say how the samples exist in the repository, and then say how they are then used. If a sample is identified in the repository, then it is an identified sample. That sample might be used in a different manner, but I have a hard time with the language on page 181 that says "truly unidentified samples," etc., etc., that is, the sample, "the repository may retain identifiers." I don't see how we can say that "truly unidentified samples" have identifiers. And so this issue, if we separate it out as to what the samples are and then how those samples are used as we had done in previous drafts, then that's fine with me.

DR. MURRAY: Even the language, I think, on page 58 seems to be self-contradictory. It would be really handy if we had perfectly clear, plain English concepts that would handle all of our difficulties here. That's not available to us because the terms—the nouns that one could apply to the biological materials as they exist in the repositories—are the same nouns that would apply to the biological materials in the hands of the researcher. You can use them. Now, what we propose on page 58 is to refer to the materials at the repositories as specimens, and the materials in the hands of the researcher as samples. That's not a common English distinction, but it might be useful if we could employ it. Would you think it useful if we employed such language consistently, which we do not now do? Would that at least help us to understand what we were saying?

DR. GREIDER: Yes. I think that the terms that you want are "samples" and "materials."

DR. MURRAY: So you don't want "samples" as it's used on page 58?

DR. GREIDER: I'm just reading what's here: There's "samples," and on 59 there's "materials." The samples are the physical things, the materials are how they're being used, if I read that correctly.

DR. MURRAY: Well, all right.

DR. GREIDER: No, now we're....

DR. MURRAY: That applies quite differently.

DR. SHAPIRO: David wanted to say something.

DR. COX: Well, I do believe the language is very important. But I don't know if we agreed on the concepts, and that's what I would like to try and get a feeling for first. If we don't agree on the concepts, the probability that we'll agree on the label is zero. So that's the first thing I would like to get a feeling about. The concept, to me, at least as I understand this, is that so long as anybody can basically take a human biological tissue sample and have it still associated with the person, then that's an identified sample. However, it's still associated with the person. On the other hand, if that sample is in a repository or wherever it is has been, had those identifiers taken off—i.e., you still have clinical information but you don't know who the person is—and you can't go back to that person, then it's not identified. That doesn't mean that there's not some hunk of that sample still back at the repository. But it's the fact that that particular sample no longer is hooked up with the person. Now the language here is very important, but the concept is a simple one. And I want to know if people agree with that concept or not, because if people don't agree with the concept, then we have a real problem. Because behind it is the sense that we don't have agreement.

DR. MURRAY: I want to recognize Eric and Bernie, but I want to insist on one thing first. Since other approaches haven't worked, let's focus on one of the two statements. Let's focus first of all on what the repository pulls. Now here we seem to be pulling these two terms in the report draft—one is "specimen," one is "materials." I would prefer "specimens," because "materials" clearly applies to (UNINTELLIGIBLE). But that's what I want to focus on right now. In the repository these human biological materials exist, and what we said in the report is that they can exist in two possible forms: identifiable, or identified, and unidentifiable. And can we focus on that for a bit? I don't know if Eric or Bernie wants to address that or not. Then we'll get to what goes to the researchers. Okay. What's in a repository?

DR. CASSELL: Well, the first step is the division into the repository and whatever the investigator uses, whatever name you're going to use. And the second step is what's in the repository—it is either identified or not identified. And there's another step that goes....

DR. MURRAY: The third step is how do we describe the various possibilities of what goes forward to the researchers.

DR. SHAPIRO: Tom, excuse me for interrupting, but could I just ask folks, just on the issue we've looked at—that is, what's in the repository—what's at the bottom of page 59? It uses the word "materials," which is fine with me, I've got no problem with it. So we're not going to use "specimens" for that; we'll use "materials," is that agreed? That's fine with me, I have no problem.

DR. MURRAY: I've no particular...(UNINTELLIGIBLE) have terms of

meaning which was so clear (UNINTELLIGIBLE) [SEVERAL TALKING AT ONCE] But we have to define it.

DR. SHAPIRO: All right, so that's just fine. I just want to make sure that's done.

DR. MURRAY: Actually, I have a preference for "specimens."

DR. MIIKE: Why?

DR. MURRAY: Because the report is about human biological materials, and that includes them both in the repository and in the researchers' hands. "Specimens," at least—you could at least stipulate that it refers to those things held by the repository.

DR. MIIKE: Tom, perhaps it would also be simple by simply moving the parentheses that says "the sample" to the end of the sentence so that it's clear that "the sample" is not referring to material but to material that is then sent on to ....

DR. MURRAY: Line 12 on page 58.

DR. MIIKE: Yes. And I also prefer "specimen." "Materials" is too general, as you say. I would think "specimen" means that it's that original hunk of whatever it is sitting in the repository.

DR. SHAPIRO: I have no view on this, I just want...how do people feel? Is "specimen" all right?

DR. DUMAS: "Specimen" is fine with me.

DR. MIIKE: It's fine.

DR. GREIDER: Fine.

DR. SHAPIRO: Tom: "specimen."

DR. MURRAY: "Specimen" it is. Eric, did you have more you wanted to say? Okay, Bernie.

DR. CASSELL: If some specific thing has been settled, I wouldn't say a word. [LAUGHTER]

DR. SHAPIRO: Can I put that on tape?

DR. MURRAY: We know where Eric lives, he's just being him. Bernie?

DR. LO: I want to pick up on David's comment, so if we're just sort of trying to clarify the terminology, I'll defer.

DR. MURRAY: Well, Eric did a beautiful job of parsing out the conceptual steps. Step one is, do we accept the distinction between whatever

(UNINTELLIGIBLE) materials we're now calling "specimens" in the repository and materials that have been forwarded to the investigator? Do we accept that as a key statement? Everyone clear about what that distinction means? Okay.

The second thing is these things in the repository, which we are going to call "specimens" consistently throughout the report, and it may make the—the language may not reflect that at every step, so we'll have to make sure we change the language appropriately—that the specimens as they exist within the repository, for our purposes we will distinguish between those that are identified and those that are unidentified. Is everyone clear and comfortable with that? Okay. So then the last step is one that David had begun to address, and that is what goes forward to the investigator. And we list them. We have, at this point, four descriptive categories we apply to this. But let me hear Bernie's comment.

DR. LO: I just want to echo David's point. I think it is important to try and clarify the terminology so it's consistent throughout the report, but I think the real ethical policy issue is these samples that are identified in the repository, passed on to the researcher in a coded fashion so the researcher can't decode it, but the code is kept by the repository, and therefore the potential exists for the researcher to go back to the repository and either ask for additional specimen—additional material from the same specimen—or to get updated clinical material information about the person from whom that specimen was obtained. And I think, as I understand from previous discussions, that this is a crucial issue for many investigators, and given the way the regulations play out, whether we call those specimens—sorry—whether we call those samples identifiable or not from the researchers' point of view has a big implication for informed consent and things like that.

DR. MURRAY: Bernie, I think you're moving us to the content of the recommendations. We will, I hope, go there very shortly. But I want to make sure we just have the concepts clear in our minds. We have tripped over these so many times that I think we're on the verge of breaking through here, and I ask Carol to carry us forward.

DR. GREIDER: I agree with the terms on page 61, using the terms "samples," "unidentified samples," etc. And again, my problem is not with this section but then how we use this section in the recommendations, because we do not use this terminology—or not even terminology—don't even use these concepts. I'm happy to agree on these concepts, but they're not likely to be used in the section on the recommendations. And that's the entire gist of my uncomfortableness.

DR. SCOTT-JONES: I have one question about this that has to do with the assumption of the division of labor, that the repository will have the samples and will be responsible for giving them out to researchers, and that researchers will make requests and get those samples from the repository. But in the example on page 62, of the researcher studying malaria, the example reads with the researcher being the person who

collects the specimens, and then the researcher would do the labeling and so forth. And are we assuming that in almost all cases there is this division of labor where the repository has materials and maintains materials, and the researcher makes the request rather than the researcher making the collection and being responsible for how the collection is stored?

DR. KATHI E. HANNA: There is probably not the best example there.

DR. SCOTT-JONES: It's not.

DR. HANNA: I mean, I think we probably inserted that one because, from our questioning of repositories and their behavior, we couldn't find very many repositories that themselves collected materials in that way. It tended to be more the clinical researcher who was just collecting materials for a specific protocol. So it's not a good place for that kind of example.

MS. KRAMER: Kathi, that example might hold if the wording was changed such that the blood was—the researcher went to the blood bank and got it.

DR. MURRAY: It's probably worth taking another minute or so just to look at the definitions on page 61. Now, speaking about these—is the audience, people in the audience, do you know what we're talking about?

WOMAN IN AUDIENCE: No.

PROF. CHARO: Tom, I got the sense that, actually, in the end everybody did understand and agree with the use of the categories that Kathi laid out, but that there are some places in the report where the terminology is not being used absolutely consistently. And that seems to me to be a text-editing thing that we need to be doing by handing it in directly to staff so that they can make those changes. Because this has been through so many drafts that it's likely there will be errors from previous versions that we've all contributed to. So it doesn't sound like it's a conceptual issue at all; it's a matter of just handing in text edits.

DR. MURRAY: Well, I wish I could agree with you wholeheartedly, Alta, but my experience has been that there has been persistent, skeptical disagreement. It sounds like it's dissipated, it sounds like we're all together, that we accept at least that the four categories of samples are the appropriate categories, and can carry that forward in the discussion. Yes or no?

MS. KRAMER: I have one question, looking ahead to the recommendations. When we talk later on about collections that are sent from the repository stripped of individual identifiers but the repository knows which hundred are in that batch, is that now—are we going to call that "unlinked" or "coded"? The repository cannot identify an individual, but ... that's going to be "unlinked." Okay.

DR. MURRAY: Unless the language actually says—look at page 61, lines 18 through 21, which I think addresses your concern.

MS. KRAMER: No, because that's exactly where the confusion is in my mind. That says, "retains information linking the code to particular human...."

DR. MURRAY: Or "where the extent of the clinical or demographic information provided is sufficient that the investigator, the repository, or the third party could link the biological information derived from the research with material from a particular person or a very small group of identifiable persons."

MS. KRAMER: Okay, so then what's a "very small group"? If a batch is a hundred, is that a small group?

DR. MURRAY: That's entirely in the context.

MS. KRAMER: Well, I think this could provide confusion later on.

DR. MURRAY: David.

DR. COX: I have a proposal, that because of this, in my view, it's not a matter of words, but the words basically make it unclear whether we disagree on concept. It's the commissioners who have strong feelings, and I'm one of them, about this—use their own words, write it down on a piece of paper and send it around so that there's no confusion from their point of view in terms of what that language is. Because as a group, the probability that we're going to work out the language issues is zero, since we've tried it about 200 times.

DR. GREIDER: Can I just say something? I think I'm the one who's responsible for this feeling among people that we're not—at least I'm partly responsible—for bringing this back up recently as an e-mail issue. And I don't have any problems with this section that we're talking about right now. Where I have problems is how we then translate this into the recommendations. And so I'm not sure that there really is a problem with the language or whatever. The thing is being consistent and then taking that forward to the recommendations.

DR. HANNA: If I could summarize where I think the disagreement or confusion continues, it is in the two top categories—I'm sorry, it's in the unlinked samples and the coded samples—on page 61, those two categories of samples. When we get to the recommendations, it seems that some commissioners want to put the unlinked samples into the unidentifiable category, and some want to put them into the identifiable category. That's where there's disagreement. I don't think there's any confusion, it's just where people want that category to go.

DR. MURRAY: Larry?

DR. MIIKE: Yes, that's the gist of it. And I don't think, whether you put

it as "unidentified" or "identified," that we're differing about how you treat it in terms of the review process. But apparently, if you call it "identified" it goes through a completely different review process. As I said in my last e-mail conversation with Carol, the bottom line was that it really didn't matter to me which way it ended up, although I prefer to call the unlinked "unidentifiable." It didn't really matter as long as the regulatory rigor applied to these is about equal no matter what you call the category, because that's the bottom line about what we tried to do.

DR. MURRAY: So I just want to see if I understand correctly, Larry, that in terms of the concept, this set of four concepts works for you.

DR. MIIKE: Yes.

DR. MURRAY: Loud and clear. When it comes to policy decisions you may wish to combine them, or different people may wish to treat them in slightly different ways. That's fine. If we get the concepts clear, that's a very, very important first step. Alta?

PROF. CHARO: I don't believe that the concepts, as you put it, can be made clear in a way that's isolated from their consequences. Words don't have absolute meanings. They have a meaning and a context. Here, the significance of calling something one thing or another is to use that word subsequently to trigger different consequences. Otherwise, you might as well call them the same thing. The only reason we distinguish red from purple is so you can sort your clothes into red ones and purple ones. Otherwise, it doesn't really matter. Therefore, I think it actually would be productive to focus on the policy questions rather than the words, and then work backwards. For example, the overall issue here is how one wants to see the stream of research proceed. Everybody knows that a large portion of the research is going to be benign, and some small portion of it is actually going to be somewhat threatening or risky. Therefore, the question is how do you design a series of holes in the system where you can stop, think, and perhaps put in protections, and where do you want those places to be? Do you want one of your holes to be that most things have to go through a body that gets a first eyeball, and then you have a fairly easy process following it because most things are going to be minimal risk, and da, da, da, da? Or do you want something where very few things wind up going through a regulatory process you try to prescreen, and then once they're in there they get a very heightened level of scrutiny because you've already prescreened for things you think are going to be problematic? It's like looking at a pipe with little narrow areas and you want to find which of the areas you're focused on. The words that we use here are primarily aimed at that first chokehold, which is, does it go before a peer review body in the form of an IRB? That's what these words are designed to accomplish, is to sort things out for into review, even if it's going to turn out to be expedited review, no consent, etc. But do they get a first review or not? And so I don't think it's actually ever going to be possible to get a kind of intrinsic, inherent, pure

definition of these concepts isolated from their uses. I just don't think anything in this world can be isolated from its uses.

DR. MURRAY: Bernie?

DR. LO: I want to continue this line of thought that the categories are important but the reason they are really important is the policy implications that flow from them. And I think one of the things that we're doing here is using categories that already have pre-existing regulations and consequences attached to them. I think we've identified what the tough cases are, and I would actually prefer that we take a look at a tough case—one I mentioned before, for example—and try and decide how we want that regulatory impact to flow. I think that I'm concerned that we're using the pre-existing categories, trying to stuff things into one category or another and settle the question of whether we think certain types of review ought to go before an IRB, ought to be able to be done without specific consent or not. And I'd rather we talked about specific cases and said what do we think is the right thing to do, and then see whether it fits the existing concepts, categories, and regulations.

DR. MURRAY: Carol?

DR. GREIDER: I agree with Alta that one of the issues is the policy, where the policy comes. And I thank Kathi for pointing out that really where the rubber is meeting the road here is the middle two categories, whether you go up to the top one with the second one or down with the second one. That's something we should discuss. Again, I'm not worried so much about what language we use, but that we are consistent throughout. And I really don't have a problem, I don't have a particular direction they should go, up or down, but what bothers me is the fact that we're very inconsistent. This whole language is laid out on page 61, and in the recommendations there is no restatement of these kinds of categories. The words that are used would suggest that category 2 that we have here on 61, unlinked samples, is now called "unidentified." I think that that terminology is obfuscating, and investigators can say they are working with unidentified samples when in fact it is possible to identify them. So I just want some kind of clear language that you can't have investigators pretending that something's unidentified when there might be some way to identify it. Then the policy decision is fine; we can talk about those. I don't have a particular bias one way or the other. It just bothers me to put in language that is unclear and so it can seem like you're working with one thing when you're actually working with something else. So if we just take this whole text on 61 and stick it in the recommendations and then be very clear about what we're doing, that will solve all of my problems.

MS. KRAMER: I basically want to say the same thing, except I'd like to carry it one step further. And I think that before we go on to the recommendations we ought to adopt, say, a working proposition: let's decide what we're going to call that second category—either we're going to call it "identified" or we're going to call it

"unidentified," and see when we get to the recommendations if it works. If it doesn't work, then we know where we've got to go back and correct it. But I myself don't understand when you—if the investigator requests the repository to strip all of the identifiers off of a batch of specimens before they're sent on, I don't understand why that still remains "identified." Yes, I know we've heard the arguments that....

DR. MURRAY: It's not. It's "specimen" in the repository; if it was identified, it's an "identified specimen." If everything is stripped and then sent on to the researcher, it is now called an "unlinked sample."

DR. GREIDER: Right.

MS. KRAMER: Not as far as the recommendations.

DR. MURRAY: If our definitions don't....

MS. KRAMER: Now wait a minute, hold on. Now what about a situation where the repository knows which hundred samples it sent but doesn't know which one is which?

DR. MURRAY: That's still the "unlinked," unless—read lines 19 through 21—unless it's so small. Unless there is enough information accompanying the sample that some party could perhaps reestablish the identity of the person providing the sample. Then we'd have to count it as a "coded" sample, according to our terminology.

MS. KRAMER: But that's where it gets very unspecific, like how much is enough information.

DR. MURRAY: Right. We don't quantify that.

MS. KRAMER: Other than that it's going to be—all right, it's going to be "unlinked," it's going to be "unidentified." "Unlinked" is, therefore "unidentified."

DR. MURRAY: That's not what I said. It's "unlinked." Treat it as linked.

MS. KRAMER: It's going to be treated as "unidentified." Oh.

DR. MURRAY: And that's what we'll talk about in the policy discussion. Now, Harold?

DR. SHAPIRO: It seems so me, Tom, what I'm hearing is that it would be a good working proposition right now just to accept these pages as written, quite aside from the examples you might want to change. And at the appropriate moment, when you're ready, just go ahead and start looking at the policy issues.

DR. MURRAY: I agree.

DR. SHAPIRO: And see if it works. If it doesn't work, we can circle back.

DR. MURRAY: I agree. I do actually think that this morning's exercise so far has been helpful in getting things straight. At least we have a shared understanding the concepts we wish to use. Eric?

DR. CASSELL: Well, I think I'll say something similar. I think you have to establish, and I won't buy into any agreement on concepts and possible language before you go to consequences, because I listen now to this discussion go around and around because of a confusion of a level about which people are talking. And unless we settle that this is the end of this level and we make sure about it, then you can't move forward to consequences. Things are what they are apart from their consequences. And things like words are very difficult, if not impossible—they are not definitions. It's either impossible or it is not impossible. If it's not, it's possible. And it's that sharp definition we need at this stage so we can accept it and then move on to consequences. Or one says it will never be impossible, and then that's a definition. But it has to be precise language at this point or no precision is possible at any further stage. It's just like the identification of an organ or a tissue or anything else—you've got to have language that positively identifies it or concepts that identify it before you move on. I can't see how you could do it otherwise, and I think the experience of this report is the evidence of that.

DR. MIIKE: It's clear in my mind, I think. What we're talking about is that "unidentified" samples and "unlinked" samples are going to be treated the same; "coded" samples and "identified" samples are going to be the same. That's what we're talking about. So the definitions hold, it's just how we apply the regulatory review process to those two categories.

DR. MURRAY: Okay. Are we ready to move to the next level? Kathi has something to say.

DR. CASSELL: That means you're taking out difficult, but not impossible?

DR. MURRAY: No, it doesn't.

DR. HANNA: I just want to add the reminder that part of the confusion is because we're trying to look at how these materials are defined in the context of research, because the regulations apply to them only in the context of research, not in the context of how they sit in the repository. The regulations have nothing to do with how they sit in the repository. So just as a reminder, it's the research use, and that's maybe why there's some confusion between this chapter and what shows up in the final recommendations—because the recommendations really only talk about their use in the research, and therefore the regulatory setting.

DR. MURRAY: Right. If you look back at Kathi's memo, do you want to describe what you were after in your point 2?

DR. HANNA: Well, I think that 2 refers back a little bit to what Alta was talking about earlier, and that has to do with that there's been some concern on part of commissioners that we aren't presenting a kind of big picture of this area of research. We're not communicating through the report whether in fact the Commission feels that by and large most of this research is going to be minimal risk, or conversely, that a lot of this research is going to be above minimal risk. There needs to be something in the report that communicates where the Commission stands on this area of research—the reason being that if the Commission feels that a lot of this research is above minimal risk, then that's going to dictate how elaborate a system of protections you want to put in place. So everything else falls out of that. The discussion and the report right now on minimal risk that appears in Chapter 5, staff have worked on it. We've tried to figure out what to say about this, and what you want to say about the concept of minimal risk and rights and welfare in the context of this kind of research, which is different from minimal risk or risk issues when you're doing invasive research or the kind of research that you're talking about in the Capacity Report. The concept of minimal risk and rights and welfare concerns is different when you're doing work on materials that are stored and far removed from the source. So we would just appreciate some clarification on what kinds of overall statements you'd like to make about this area of research and what kind of language might be useful to an IRB that is trying to decide whether this is minimal risk or not.

DR. MURRAY: Kathi, I'll just look for guidance here from the commissioners. Would you want to discuss this issue in generous terms, or would it be better to turn to those passages in the context of Chapter 5, which addresses the issue of minimal risk? Is there a sense from members of the Commission as to the most efficient way to proceed? Well, hearing none, do you want to talk about the issue in general terms or a given interest in getting them down to brass tacks? Do you want to turn to the passages in Chapter 5 in our recommendation (UNINTELLIGIBLE)? That addresses the issues of minimal risk.

DR. HANNA: Can I just add that the reason why this is important following on the previous discussion—and I think you have to have this discussion before you can make your decision on number 1 in my memo—is that you have to decide how protectionist you want to be? And how protectionist you want to be will tell you whether you're going to put unlinked samples into identifiability or unidentifiability. So the two discussions really do feed on each other.

DR. MURRAY: Bernie?

DR. LO: I think it is very important to have a general sense of whether we think most research involving stored tissue samples is minimal risk or not because it obviously is a key term in the regulations. I would like to suggest that the answer is yes, but with a big but. I think that most research is minimal risk, but there are a lot of big

buts. And I think if we could agree on that and try to define IRBs and the types of research they need to watch out for, we will have done a big service. I mean, if you think about most of the things that are done, samples from persons with specific conditions are looked at for certain conditions. Often the people who donated the sample have the actual condition; sometimes they don't. But my sense is that most people don't think that type of research per se is particularly risky. But there are certain types of research that are, and I think we tried to introduce this concept of sensitive studies. I think that my concern with the report as it now stands is that in our effort to say that most of this is minimal risk we downplay the types of research that probably aren't minimal risk. So I think that if we can agree that it's mostly minimal risk but we ought to define more precisely those areas where IRBs and investigators ought to have a lot more caution, we might have pushed things a big step forward, because as it is now there's just a lot of confusion. You heard, again just yesterday the notion that, well, you guys seem to think that any type of DNA-based research is more than minimal risk. And I think that that's such a sweeping statement, but it really does color what a lot of investigators and IRBs now think.

DR. MURRAY: Bette and Alta.

MS. KRAMER: Bernie said what I wanted to say. I think we ought to adopt a statement one way or the other and then proceed from there.

PROF. CHARO: I agree with Bernie that most work in this area is likely to be of minimal risk to the people whose tissues are used. I think there are going to be several different ways in which that low risk can be identified, and it's probably worth our while to list them. Some of them are topical—that is, you're dealing with characteristics that themselves are not particularly controversial, stigmatizing, or otherwise upsetting. You're looking for things that have to do with coding for hair color; I doubt that it's really going to be significant in the context of risk to anybody. And a lot of research is that type. The second way in which things become minimal risk is not based on what you're working on but on how you do it and how you make sure that certain risks don't come to pass. That is, you work on the probability rather than the magnitude of possible harms. So on this score it's a little bit like with the Capacity Report: there's a toolbox that can be used in research protocols to ensure minimal risk. One is the creation of appropriate rules ahead of time about how you're going to decide if you would ever go back to the original tissue source to tell him or her something that you had found. Most researchers certainly don't intend to do this, but occasionally some result comes up that raises questions in the researcher's mind about whether this needs to be done. Prospective planning about when you will or will not do that lets an IRB assess whether or not there's a specific chance of this happening. David Cox has spoken often about the value of repositories, even helping in this kind of endeavor, since often to go back to the tissue source would involve cooperation from the repository anyway because they're the only people who will hold the key to the links between the

researcher's sample, the repository's materials, and the name and address of the tissue source.

The second thing has to do with the kinds of protections against breach of confidentiality of the work that the researcher is doing. And that's a real issue because there are many institutions in which medical records have to have test results recorded, regardless of whether they're in the context of clinical care or research care, so that research results are being intermingled in a record that's available to other people. And this is the kind of thing where the Joint Committee on Accreditation of Hospitals would actually be able to do something useful in order to help sort out that problem and allow research information to be isolated in a way that maintains privacy. Finally, you can take a look at the kind of information you're generating and the kind of population you're studying. If some of the harms that you're worried about have to do with things like a breach of confidentiality that leads in turn to loss of insurability for health insurance, for example, you're dealing with a population that's drawn from a group that is covered under a group policy. The risk is then much lower than if you're drawing from a population insured by individual health policies. And most people are covered under group policies, but they're not individually rated. Some degree of attention to that I think would be important. These are all the types of things that can go into a protocol that can make something that otherwise might not be minimal risk become minimal risk because you paid some attention to ways that can be accomplished. If we list those kinds of tools we can also suggest that most protocols can be rendered minimal risk in one fashion or another.

DR. MIIKE: I think that through the course of this study we've been distracted by how we treat the materials and we've not paid enough attention to the informed consent process. I think if we're talking about greater than minimal risk, that's the area where you put the protections in. I personally think all this issue about confidentiality insurance is overblown. Everybody is worried about that, but there's very few real cases to me in a systematic fashion that makes me worry that it rises to the level of primary importance in this area. So that when we talk about minimal risk or greater than minimal risk, the way I would view it is, of course, we deal with the way you treat existing specimens; but I've said from the beginning that we've got to address the issue about the current informed consent process in clinical collection of specimens. And my proposition has always been that the easiest way to do it is you sign twice. Just pull out that general authorization for clinical use that's buried somewhere in that clinical consent form, stick it at the end after you sign your clinical consent form, and sign again where it says, "In general, I agree to make my tissues collected available for research."

So I think that if we're going to be talking about protections and levels of risk we've got to turn back toward the informed consent process. It seems to me, and you can correct me, the scientists in this group, that the areas in which we're going to be dealing with greater than minimal risk are basically going to be in those areas where

people are going to have their specimens collected in a research protocol and not in a clinical setting, and that's the primary area in which people's really valid informed consent can be obtained.

DR. MURRAY: I want to just see if I understand some of the points that have been made in the last couple of minutes. First of all, there seems to be a sentiment that most of the research involving human biological materials either is minimal risk or could be made to be no more than minimal risk with appropriate care—Alta's toolbox. Larry is then talking about one of the means by which we protect the rights of subjects, that is, by informed consent. That becomes a policy response and a means of protection. Those are separable points, both important. Am I clear? Am I capturing what was being said? All right; I just wanted to make sure about that. I know Steve had his hand up. Anyone else? Steve, then Bernie.

MR. HOLTZMAN: What's been somewhat unclear to me in this line of discussion we're going down is the following one of thought: the way we've used our classification with respect to identifiability results in the overwhelming majority of samples in what I believe are the overwhelming majority of studies being considered identifiable samples. Hence, the way the regulation operates is it puts you into the gambit of the reg. We're now saying, "Hmmm...but the majority will be minimal risk," and I think that's probably true, but you still are in the pathway where you have to go through the four-part test.

So all that minimal risk gets you is the potential for expedited review. It doesn't get you outside of the issues of whether re-consent is necessary, the practicability tests, and whatnot. And therefore it is striking that in Kathi's letter she's got it exactly right—if you're heading down this pathway you then ask yourself about the consequence, and you say, "Maybe I've got to get rid of the practicability requirement, because if I leave the practicability requirements, this will be tantamount to having to go back and re-consent." If you look at our recommendations on pages 203 and 204, you will find that that's where it comes out. So I'm not sure what this gets us by focusing on the fact that they are minimal risk unless you're going to draw a consequence from it.

DR. SHAPIRO: That's point 3 in Kathi's letter, as I recall.

MR. HOLTZMAN: That's exactly right. So again, it comes back to that it doesn't matter what you call it, and I think Alta is exactly right: it does matter what you call it because these are the consequences of calling it the way we've called it.

PROF. CHARO: Steve, I absolutely agree. That's why one of the very initial questions that needs to be answered is whether you want to use a system that refers a large bulk of the research to an IRB for a pre-review. Right? Because the question is how worried are you about the subset of cases that really deserve some extra

protections and some peer review. And it may be that we can't answer that question, we can't balance the burdens of having IRBs review things that in fact turn out to be fairly risk-free as opposed to the value of having them catch the ones that are risky. We may not be able to answer that until we get further down into determining exactly what level of protection will be imposed on the ones that go through the system, including protections that may be excessive by virtue of the way the regulations are phrased.

So I don't think we can actually get back to the first question of whether or not we should have them all go into the IRB to begin with until we see how flexible it is at the other end and how efficiently we can clear out the problem-free protocols.

MR. HOLTZMAN: Right.

DR. MURRAY: Bernie, then Carol.

DR. LO: I want to try and add a couple of points to the discussion, which I really agree with. I think people are pointing out that there are a lot of key points in this and minimal risk is one, whether we're going to get consent is another one, and whether the practicability criterion is going to be retained or modified. I would like us to focus on what's going to be our bottom line in terms of what kind of oversight and what kind of regulations for what types of research.

I want to try and point out that in our two reports it's important for us to be consistent in the way we think about minimal risk. With the other report on persons with mental disorders we took a very strict view of minimal risk. We said there's going to be minimal risk and not minimal risk, and things that are a little bit more than minimal risk but aren't minimal risk. I think there are going to be some attempts, because of what flows from the regulations, to try to put things in that category that on first glance might not fit in that category.

One of the things I think we should think through is to what extent do we feel obligated to retain the current regulatory structure with certain concepts being absolutely crucial in terms of what gets reviewed, what needs informed consent, and the like. There are pragmatic arguments and there are conceptual arguments. Pragmatically, we started out many meetings ago saying look, just sort of try and rewrite the regulations. It's a herculean task. To the extent that we can use the existing framework, it's going to be a lot simpler. On the other hand, it seems to me that if the existing categories and the way these are linked to regulatory provisions really aren't quite right for DNA testing on stored tissue samples—remember, these regulations were written for things like reviewing medical records of your last 50 cases of a certain type of operation—it's not to me automatic that those categories, as helpful as they may have been, are going to be exactly the ones we want to use to tie to certain regulatory things here.

My own concern is that by being wedded too tightly to existing

categories and the way those categories play out in the regulations, we're going to end up with putting things in boxes where they don't really belong, because at the bottom we don't want them to be in the category of "must get full informed consent." I think we have to think through whether the gist of this report is a conceptual report to help IRBs and investigators who are truly perplexed about these issues—what are they supposed to do, do I have to go to the IRB, do I have to get informed consent—to help them think this through. Is that going to be more valuable than saying, look, we can tinker with the regulations so that you can solve most of the problems?

I think that if we can reflect back on our experience with the other report, we ought to sort of see if we can learn from that how to make the second report of the two go a little smoother. But I would just be a little concerned that we not feel ourselves too tied to concepts and the links between those categories and regulations that may be counterproductive at this point.

DR. GREIDER: I agree with what you said, Bernie, and I agree with what Alta said, and I agree with what Steve said. Here is my problem. Alta says that we should think about what the consequences should be. So if I think about these four categories that we have of our samples and how they're treated, I'm happy to take the first two categories and treat them one way and the bottom two categories and treat them another way. But in order to do that with our current regulatory system, what happens is that our recommendations now say that those top two categories are called "unidentified."

I think that giving the message to investigators that these two samples are the same and are "unidentified" makes them think in a certain way—that they can fool themselves that these samples really are unidentified when they're not. And I would like the investigators to realize that they are really two different things and yet have the regulations come out the same way. And so that's my problem: that the way I want the consequences to be, it's difficult right now to find language to fit those two things into the same thing without making it clear that they are very different things.

DR. SHAPIRO: Carol, I just want to make sure I understood what you just said. It was that if we take the first two categories of samples, currently called "unidentified" and "unlinked," that in your own judgment you would like to treat these in the same way, but have investigators conscious of the fact that they aren't quite the same. That's the aim, as I understood what you said.

If that were the case, it seems to me there's a simple answer to that problem—namely, you just never combine them, you just keep on using two words. So you just say "unidentified" or "unlinked" have these regulations, "identified" or "linked" have those. That seems to me a reasonable solution if that were the problem. I just want to make sure I understand.

DR. GREIDER: That's my major problem.

DR. SHAPIRO: Thank you. I just wanted to understand.

DR. MURRAY: I think that clarifies for me Carol's concern. I think, Harold, it's a very elegant solution, really, to just keep labeling clearly at every step each of the categories we think belongs in each particular policy response.

I heard a different concern expressed—let me see if I can try to put it concisely, and tell me if I understand it correctly—that given that most of the research with human biological materials will either be minimal risk or can be made minimal risk with appropriate, readily available measures, and given the current regulatory scheme, so long as they are either in our categories of "coded" or "identified," an investigator would be put through a fairly extensive process in order to receive approval for the research or might be made to go in and take measures that might be disproportionate in order to get, for example, re-consent in order to be able to use those samples. Do I understand that? Is that the concern that I've heard expressed I think by Bernie, maybe by Steve, and maybe by Alta?

MR. HOLTZMAN: It's precisely that. If you're getting specimens from the Corials of the world, in our terms those are "unlinked" samples. They also, for that matter, may or may not be "unidentified." But in the majority of instances, when you're going to the pathology department what you're getting is a "coded" sample. Now what we have in our report is OPRR's interpretation that a "coded" sample is "identifiable" according to OPRR and therefore triggers the entire consent process.

Six months ago I asked whether or not we could ascertain whether most of the researchers in the United States share that interpretation. I don't know if we ever got an answer to that question. So, therefore, I don't know as we're writing this what the practicable implication is because we never, to my knowledge, found out what the practice is.

DR. MURRAY: Kathi?

DR. HANNA: We actually did ask some of the big repositories.

MR. HOLTZMAN: Kathi, the repositories, I'm familiar with their practice. I'm talking about most of the stuff going on, which comes from the pathology departments.

DR. HANNA: And your question is, do we know whether they're being forwarded to the investigator as "coded" samples?

MR. HOLTZMAN: Yes, number one. And if so, are they being subjected to IRB review and meeting the four-part criteria? Do we know that?

DR. HANNA: No. We would have to do a survey of investigators to find

out, in fact, how they submit. We have no way of knowing from the IRBs either, because if it doesn't come to the IRB they have no record of it.

MR. HOLTZMAN: That's right; you'd have to go to the pathology departments.

DR. HANNA: Right. I would just add one other thing here, which is that there is another consequence of calling "coded" samples "identifiable." It doesn't necessarily mean that all of those protocols have to go to an IRB. It could also mean that the investigator can make a decision to unlink the samples. Yes, request the samples in an unidentified way, whereas before he or she might have not thought about whether it mattered to have them coded or not.

MR. HOLTZMAN: That's certainly true. My question is about research as conducted now.

DR. MURRAY: And Elisa Eiseman was nodding knowledgeably there. I don't know, Elisa, do you have anything further to add in answer to Steve's question?

DR. ELISA EISEMAN: No, I agree with what Kathi said, that that's a really hard question to answer.

PROF. CHARO: First, I think there may be one easy way to get a partial answer to the question, and that's to contact PRIM&RB, that is the Public Responsibility in Medicine and Research Board, because they work directly with investigators and IRB members and can probably give us a fairly good idea of how the regulations are understood in the world so we would know how much our advertisement of OPRR's current understanding is going to shake things up out there. But in some ways this is not the main focus of our discussions, because we do not control OPRR's current interpretations; they can change them if they want. But since they're the lead regulatory office in this area, for better or for worse, their interpretations are going to be given great deference.

What can be within our purview is to suggest ways in which the current regulations that don't have much interpretation could be interpreted, as well as to make recommendations for specific changes. For example, having something go to an IRB for a first prescreening does not necessarily turn into an incredibly burdensome procedure if (1) it's handled in an expedited fashion, and (2) if the protections that flow from those things that can be rendered genuinely minimal risk are not disproportionate. And that means a focus on the meaning of consent and, specifically, whether what was described to us at one of our meetings as an opt-out as opposed to an opt-in procedure is an adequate substitute for consent. It's not the same thing as consent, but it's an adequate substitute in light of minimal risk in that it answers the question of paying respect to people's personal choices but is less than the ordinary kind of consent that we associate with things. That might be one avenue to work on.

The second is an understanding of practicability that takes into account costs, time, response rates, etc. We've got some possible avenues for discussion.

And one final comment on the point about whether or not opt-out as opposed to opt-in is an appropriate level of respect for people, where opt-in is what we ordinarily call consent and opt-out is clearly a new beast, not consent, something else. I'd point out only that for those of us in law, we're familiar with the history of the doctrine of informed consent. It grew entirely out of a set of circumstances having to do with physically invasive phenomena; that is, I touch you without your consent in a way that's harmful or offensive. That's the origin of the doctrine, and its extension into non-invasive areas such as purely informational areas even in the medical malpractice realm was a very substantial expansion of law and has created theoretical problems that we're coming up against here. And then in the regulatory regime in research we saw the same thing—the same notions of consent and the same notions of entitlement to give consent were given to both invasive and non-invasive research.

Non-invasive research is the new wave. There are a lot of privacy concerns out there, may be best dealt with under the rights and welfare language, but I think it's up for discussion whether an opt-out procedure is an appropriate level of personal respect and opportunity for choice in non-invasive areas, like research on excised tissue.

DR. MURRAY: Alta's comment actually brings us to point 3 in Kathi's memo, where she asks about practicability and opting-out. So Kathi, would you say what you'd hope we do in response to that inquiry?

DR. HANNA: Well, the issue of practicability actually came up about six months ago in staff discussions, and we weren't clear the direction the Commission was going in terms of labeling and how large the flow was going to be to the IRB. When we went back and looked at the four conditions that have to be met for waiver of consent, we thought that one way of trying to decrease the volume, if that's in fact what you want to do, would be to say that even if you're going to send all these, because if you do call "coded" samples "identifiable" you are now going to be sending more protocols to IRBs, because that is clearly not the way the entire scientific community is viewing those protocols. So you've already increased the volume of protocols going to the IRB. Now they have to make a decision about whether consent is required and they have to meet the four criteria, and all four have to be met. And it occurred to us that if, in fact, in this area of research—that is, using biological materials—if it is minimal risk and there are no concerns about rights and welfare, then would it make sense to then drop the practicability requirement and instead offer an opt-out mechanism, so you would actually waive consent after the first two conditions were met?

And then for those studies where you might have concerns about the nature of the research, it for some people might be objectionable, then you would give

the opt-out mechanism just as an extra measure of protection. But the opt-out mechanism kicks in only after consent has been waived. We just floated that on e-mail to see how people reacted to it because, as Steve said earlier, of the direction the report is going in, and it might be the way you want to go, but you're building the volume exponentially of protocols that are going to go to IRBs that are going to have to not be able to waive consent even if they are minimal risk because of the practicability requirement, therefore requiring consent or re-consent on a huge number of studies. The question is, is that what you want to do?

DR. MESLIN: Yes, Steve?

MR. HOLTZMAN: I think you're right, Kathi. And I want to make clear to the Commission that from my perspective this is a very textured and layered landscape. As we think about going forward in the context of major medical research institutes, where people recognize that that which is collected in the clinical context is likely to be used for research, you're going to see much more robust consents, and I think we will all applaud that. I'm thinking of a relationship we set up with the University of Pittsburgh Transplantation Center, where we knew we would be establishing a tissue bank—very varied layer of consents.

But you have to keep in mind the whole landscape of research here. There are large numbers of samples that are just coming into community hospitals that have tissue banks, that will be brought in where you're not going to have all of the apparatus involved, where you're going to just have the local doctor and local pathologist and you're going to be getting those samples.

And so I just want to caution us to keep in mind the broad range of examples not only on the go-forward basis but also in terms of what we're saying with respect to a repository that currently exists with millions and millions and millions of samples. What when we're finished with this will be the consequence in terms of cost and practicability of doing the kinds of research that most of us would say are minimal risk and are not a problem, and which I believe we heard in a non-scientific but nevertheless perhaps meaningful sampling of public opinion, will be that most people thought it was good that those sort of samples were being used to that end.

DR. HANNA: Let me just add that this suggestion only applies to existing samples, obviously. So don't get confused. Obviously, you can't obtain a sample from a living person without their knowing you're doing it. This is only for existing samples.

MR. HOLTZMAN: No, I realize that. But there will be stuff that falls in the category of existing in the future, Kathi, right?

DR. MURRAY: Further thoughts about this issue? Bernie?

DR. LO: I think this is a very important topic and I'm glad we're pursuing it. I wanted to make a couple of brief remarks relating back to what people have said and then try to introduce some new concepts. First, with regard to Alta's reminders about the history of informed consent, while I agree with what you said about the development of the doctrine of informed consent in a treatment setting, I think the research setting is really different and that it's not just physical harms but being a research subject without knowing about it. Having been involved with some investigations of the human radiation experiments, in which people were subjected to radiation in really trivial doses that was not a physical harm in any meaningful sense of the term—but it was an offense in that they were used without knowing about it and without their permission, and they were outraged. So I think that in a research setting we should be paying more attention to non-physical harms than we would in a treatment setting.

Second, Steve brings up a really important point about existing samples and future samples. One of the things that concerns me is that we should really be looking toward the future and encouraging investigators under IRBs to develop consent forms that are really more meaningful than current consent forms. I think Larry brought up the really important problem of what to do with samples that are going to be collected in the future in a primarily clinical context and what we can do to get away from these blanket consents that are signed on admission or as part of the surgery consent form.

I'm willing to treat existing and future samples quite differently. I think Steve's point, that there's a lot of samples there, it would be a shame just to not use them by making people get specific consent. But what I would like to see linked to that is a real commitment to saying let's make consent in the future much more meaningful than it is now. There's a lot of exciting work going on out there on how to do that and that's not in our report now and I think it's a real lack. It's actually not taking up an opportunity to really take the lead here.

Finally, Steve brought up a point about community hospitals participating in repositories. I remember we heard many meetings ago from women with breast cancer saying that if they went to their community hospital for a mastectomy, it was important for them to know that their sample might be used in future research and they didn't want to be excluded. I think that's a good point, and I laud them for their altruism. But I think what they need to understand is that we're not just talking about using their samples for breast cancer, we're talking about using it for Alzheimer's, drug addiction, and a whole bunch of other things. To me, that's a misconception about what's going on. I think for people to think that it's going to be used to help researchers find the genetic cure to their specific illness is not what we're talking about here. I think Steve was very eloquent in giving us a sense of the big picture here. We're talking about lots of other diseases, some of which are diseases they'd probably say, "Yes, go ahead and use my sample for hypertension or something," but there also may be researchers who by the same process,

unless we can be creative here, might want to use it for research on aggression, research on drug addiction, research on all sorts of other things that people might be a little less comfortable with.

So I think it is important, as we think about trying to remove unnecessary regulatory burdens from the majority of protocols that are proposing to used stored tissue samples, that we also be very clear about the number of situations where we really want to make exceptions and to get researchers to think very hard to make sure that they're not in one of the exceptions.

DR. MURRAY: Bernie, just to bring this around back to the conclusions and recommendations. We do try to identify a category of research that would be—we've used different labels for it, controversial, sensitive, I don't know that we have the right label for it, nor do I want to spend a lot of time deciding on what the right label is—but we do want, I think, to signal that such research does happen, is possible, but also that it's likely to be relatively—my conviction, tell me if I'm wrong—likely to be a relatively small percentage of all the research projects undertaken. Is that a reasonable empirical presumption or not?

DR. LO: Yes. I'm willing to agree with that. I don't have any better facts than anybody else. But I think that if the gist of what we're saying is that we only remove unduly burdensome regulations from the vast majority of projects, it seems to me it becomes very important then to be very clear that on the other hand it's extremely important to make sure that we've fleshed out those categories where we don't think the streamlined process is appropriate, and then to decide what level of oversight we're taking. For a lot of this, it seems to me it's just consent. If there's a sensitive, which is one of the adjectives we've used, topic, maybe an opt-out really isn't good enough and you have to use specific consent for the types of research that we've listed. So we have a lot of, in Alta's metaphor, tools in our toolbox. My concern is that we just identify a big category of saying we've got to take these, consider them apart, and then decide what sort of additional precautions are triggered by things in that exception category.

DR. MURRAY: We have a couple of policy possibilities there; we have more than two, but just two obvious ones. One is to say, look, we think this is likely to be so infrequent and to be offensive to so few people that we're just not going to create any special rules to deal with it at all. That's not the direction we're heading. The direction we're heading is to work somehow into the process a signal that would indicate that sensitive research is at issue and that it may require some different sort of reviews and different sort of response. Are you happy with that second track, which I believe is the track we're trying to take?

DR. LO: So, for example, just to be very concrete, if we're going to use for existing samples the clinical consent form as meaning anything, we probably should say it doesn't apply if it's a sensitive topic. That it's presumed that you would consent to

have your breast cancer specimen used for investigation of breast cancer or other cancer or other diseases that affect women, but not for the genetic and ethnic bases of violent behavior. That's a totally different area.

DR. MURRAY: Right. Rhetaugh?

DR. DUMAS: I think I agree with Bernie. I'm not quite sure. It seems to me that there is the issue of rights and prerogatives of the donor and then there's the issue of the potential for harm or discomfort. And I think we need in this case to separate those two, because I would be less worried about potential for injury, harm, or discomfort in a sample that's been disconnected from its donor for years. I would have a hard time really deciding what, in addition to stigmatization or bad press, could be included in that. But I resent having people use part of my body, my being, without my permission and without my even knowing that they stored that sample.

So I think that the issue of rights and prerogatives of donors is something that we need to make sure that we give attention to. And I think we have. I think the issue of informed consent is a very critical issue in that regard, knowing full well that there are some cases in which this is not going to be possible. I think we need to spell out very carefully the conditions under which informed consent is possible and where we would insist that it be obtained.

PROF. CHARO: Rhetaugh and Bernie both, I'd like to ask you to consider the following and tell me how you react to it. Imagine that somebody wanted to use an opt-out procedure in lieu of consent, so what they did was send letters that had a notice that guaranteed that the letter was actually received. This way there's not an issue of letters that never arrived where they were supposed to arrive. Okay? This may be unrealistic because of cost, but just imagine it. So they send a letter that says we need to use your tissue for the following kind of research—obviously, it's your prerogative to say no—please contact us at our expense by returning this self-addressed, stamped envelop to say no. Would that be sufficient? Or are you advocating more than mere notice and an opportunity to decline, but an actual entitlement to give an affirmative yes?

DR. DUMAS: I have two answers to that. In relation to the letter, I'd want to know whether or not when that sample was collected I signed the consent form.

PROF. CHARO: No. This is in a setting in which we're going to assume that you've never prior to this moment contemplated or given authorization for some kind of research use. This is coming out of the blue to you.

DR. DUMAS: Yes, the letter would be adequate.

DR. MURRAY: Bernie?

DR. LO: I would say it depends on the study. If I had had an operation for pancreatic cancer, which runs in my family, I would be delighted to have that sample

used, and for any other type of cancer I would probably say why did you even bother, go ahead and use it. But I can think of a lot of studies that I would have said no, I won't give affirmative consent, I want to hear more about the project. So I think it's very dependent on the nature of the study. I'm willing to say to most of them that's fine, or that consent form that was buried in the surgical consent was probably okay. But I want to hold out the exceptions.

PROF. CHARO: Do you think an IRB is capable of making that judgment of when it would be appropriate to use opt-out as opposed to a full consent?

DR. LO: I think they would be greatly assisted if we could develop both some examples and guidelines. I think just to throw it back to the IRBs is asking them to do a lot, and I think they're saying this is tough. But I think we can all put our fingers on things. If someone was going to use that sample for combining my cells with cows to be cloned, I would be upset that they didn't tell me about it and didn't give me a chance to consent.

PROF. CHARO: But it's not about not being told, it's about whether or not you opt out or opt in.

DR. LO: Yes, I would want to say that you shouldn't—because we all know, I leave all kinds of mail. I don't return my driver's license reapplication on time, so the fact that I didn't return it doesn't mean I didn't want to do it.

PROF. CHARO: Got it.

DR. MURRAY: Remind us of that the next time you offer to drive us anywhere. [Laughter.] Kathi, then Steve.

DR. HANNA: I just wanted to remind the Commission that a long time ago you made the decision that you were going to assume that existing consents that were obtained in the clinical setting were inadequate, inappropriate, non-existent, or whatever. And so the reason you I think then progressed in this more protective fashion was based on that assumption. We've actually seen some consents from institutions that collected materials 10, 15 years ago in a clinical setting and they were quite clear, and I would say an IRB would say it was very clear in there that it was a separate line they signed or whatever. So all of this has been based on the assumption, which might very well be true, that existing clinical consents are inadequate. But I heard Alta say that in lieu of consent, well there was technically a consent form signed, we just don't know the adequacy of it, and in fact an investigator could pull those consents and present them to the IRB if he or she felt that they really were applicable.

DR. MURRAY: Kathi, just to amplify that. I looked at samples 15 years ago of such consent forms for research I was doing then about gifts and tissues, and there were separate lines, there were signatures on separate lines, the language was

relatively clear that you were donating your tissue, usually it was for research or education or both, not just for research. But it was also pretty clear that it was extremely generic and I had considerable doubt whether people even carefully read what they were signing when they were signing it. I have some close family experience where someone signed such and then immediately after had no idea they'd signed it. So the moral significance of these, even though there may be signatures that would look like clear pieces of paper, are, to put it back in the category, that we shouldn't assume that they were the full sort of fleshed-out consent that we regard as ideal, but perhaps not necessary for our purposes. Steve?

MR. HOLTZMAN: I had a response to Alta. But on the second point, I've given at least a dozen talks to various audiences in the last year on this subject, and I always start off with, "How many of you have had tissue taken in a surgical or other kind of medical context?" Over half the audience, it seems. "How many of you remember signing a consent to research?" Nil. So.

Alta raises the point of respect for the individual and their choices, and the notion that even if we are not our body parts there is a sense of identification with how they are used and in wanting to know how they are used so that you would not be complicit in kinds of research that you think would be offensive. And I think we all acknowledge, and in fact the regulation acknowledges, that that is an important, important value. What the regulation also acknowledges is that there are two sets of values at stake here—those, let me simplistically call them autonomy rights, and the social utility rights. And the way the regulation struggles with it is it says if I can bring down the potential for harm sufficiently through rendering the sample unidentifiable, then the social utility value will trump the autonomy right. Okay. So if we are going to now say with respect to existing samples, against a backdrop in which those consents for all intents and purposes don't constitute true consent, that we are going to use a concept of identifiability that is very broad, effectively what we are doing is saying the autonomy right now trumps the social utility right.

DR. MURRAY: Let me just tell you what our parameters are. We have something like nine minutes left for the conversation at this stage, at which point we're going to take a break and I'm going to turn it back over to our chairman. Kathi has an issue she wishes to get as clear a statement as she can on from the commissioners, so I'm going to ask her to put her question.

DR. HANNA: As you know, this next draft is the draft that will go out for public comment. So although it won't be perfect, we'd like it to be as close to where the Commission wants it to be as you can get at this point. What I really need to hear is where people stand on this practicability issue, because the other discussion can be changed in the draft now to reflect Carol's concerns and confusion about the language. A change in issue number 3 having to do with practicability would require that we

change some of the recommendations in Chapter 5 and then reflect those changes throughout the report. So I need to get a sense of whether we should go ahead and try that approach before public comment or not.

DR. MURRAY: Carol?

DR. GREIDER: This is just to clarify that what we're talking about is on page 220, the flow chart, when you're talking about waiving the practicability when you say those four items. So the question is, will the research in its entirety involve greater than minimal risk? No. So this is now minimal risk research. And then the first thing is, is it practical to conduct the research without the waiver alterations? That's the one that we're talking about suggesting we should not have for this category. Is that fair?

DR. HANNA: Right. But that would not then drop you down to the rights and welfare argument. The way this flows....

DR. GREIDER: So that would just be gone, and then it would just go directly to rights and welfare?

DR. HANNA: To rights and welfare, right.

DR. MURRAY: Bernie?

DR. LO: Steve pointed out that any time we're talking about regulating research we're balancing conflicting values—autonomy versus long-term benefits to society. I would rather see that balance made not on whether it's practical or not, but on—and it's called rights and welfare—on how important is it that I knew I was going to be a research subject and did I have a meaningful chance to say yes or no. I'm willing to say that I think that's the key consideration. And if it's on a topic that is really benign and straightforward, we shouldn't burden people with the practicability requirement.

But when I come back to whatever protection was in that practicability requirement I would like to see a beefed-up "rights and welfare" that really looks at certain types of topics with a lot more scrutiny. But I think it's misplaced to think that I'm getting protection, because it's going to cost the investigator a lot to send out consent forms. It seems to me that's a very awkward, cumbersome, and misdirected approach to trying to protect subjects.

DR. DUMAS: I agree.

DR. MURRAY: You want to say more, Rhetaugh?

DR. DUMAS: No, I just wanted to agree.

DR. MURRAY: We have a yes from Rhetaugh. Larry?

DR. MIIKE: Well, on the specific question, I think we should just send out the draft the way it is without alteration of the practicability issue. It seems to me

that if we go down the flow chart, the troubling one to me is rights and welfare. It is such a nebulous concept that I don't know where you draw the line on that. What is the meaningful application of that? I think that's where we're going to get hung up.

Overall on this project, I look at it the following way. We've made our decision about what is "unlinked" and "unidentifiable." It turns out, from what Steve says, that that just excludes a very small piece of the universe and the rest of it is still going to have to go through the review process. So what I'd like to do is to send this draft out and see what kinds of reactions we get in terms of what we're trying to do within the current regulatory structure and whether that is a feasible way of protecting individual rights and still allowing research to go forward. And then I think our choice is going to be, can we still tinker around with the current regulations to make a better balance or are we just going to have to dump the current paradigm of the regulatory structure and come up with something of our own? I think the only way we're going to know that is to send this draft out and see what kind of reactions we get.

DR. MURRAY: Larry, I actually came to a different, for many of the same reasons, I've come to a different conclusion. And that is, to find a fully fleshed-out public reaction, this might be a particularly appropriate time to plug something new that we want talked about—to see whether people are keen on it, hard on it, or think it's a wonderful idea. If they reject it, that should tell us that maybe we need to rework the whole structure. I guess I've been thinking, what's the purpose of the public review, and it's to give us feedback about what we think the most appropriate steps are.

DR. MIIKE: But what is your major change aside from dropping the practicability issue? What is our major revision?

DR. MURRAY: There will be other changes. The notion of dropping the practicability requirement and perhaps substituting some sort of opt-out, or at least offering the possibility of an opt-out procedure, is novel, as I understand it. And I would actually be very interested to know both how the public responds to that and how investigators respond to that. I'm not committed to that one way or the other. I'd be interested in what other commissioners think about this. Bernie, David, then Alta.

DR. LO: To follow up with Larry, I agree with you that rights and welfare is a pretty nebulous concept. I think one of the things we can try to do is flesh that out with some general guidelines and specific examples. I'm wondering if we should try and have a compromise, because this report has been gestating a long time and it's getting to be almost past due now. I thought Kathi's memo was very helpful in terms of signaling things that we should think about. And if we put this up on the Web, it should have a cover sheet saying these are particular topics that we would like public feedback on. So if there's a way to try to do something with the practicability issue that says this is a proposal that we're just thinking about and we'd particularly want your thoughts on it. But I thought the discussion today was very rich and ought to be incorporated in

whatever gets put out on the Web.

DR. COX: I'm responding specifically to number 3. Kathi asked whether the practicability requirement for waiver might be dropped for studies using existing samples deemed minimal risk and posing no threat to rights and welfare. I support that approach.

DR. MURRAY: And David, on the issue that Larry and I were discussing, would you want to see the notion of dropping practicability and introducing the notion of an opt-out? Would you like to see that in this next draft, or would you rather leave it out?

DR. COX: I support number 3 in the next draft.

PROF. CHARO: I'd love to take the idea out and see how people react to it. I also think realistically that, once again, we shouldn't constrain our imaginations but we should constrain our expectations when it comes to changing regulations. It might be valuable to put out in the draft two things: one that says we're very interested in this idea that would actually require a regulatory change, but short of that, there's a second idea we'd like a reaction to, and that is that within the current regulatory structure—which will remain for some period of time an interpretation of practicality that acknowledges that if an investigator plans to use a population that is likely to have a substantial portion of it difficult to find or with exceedingly low response rates, not that they are dissenting but that we just can't find out what they want—that these constitute the basis for a finding of impracticality that the IRBs can work with and that the IRBs might want to then impose an opt-out notification letter rather than simply waiving consent. That's at their own discretion.

But I'd love to be able to run both those ideas up the flagpole since it may turn out that it makes sense to recommend stages of things—one is an interpretation of current rules for IRBs to use while regulatory change is being planned. Finally, on rights and welfare, Larry, I think fleshing it out is important. I did a literature review and found virtually nothing on it. But at a minimum, I think we can add the following things to the content. First, there are rights that people have by virtue of state law that the Federal government is not necessarily aware of that the local IRBs need to be aware of, and if something violates their rights as given under state law, clearly that's relevant. For example, there might be a medical privacy law that affects the ability of the researchers to continually go back and ask for abstracts of medical records. We've actually not found one that was a complete obstacle, not one that couldn't be passed. On the welfare, I think that's a good place to pick up some of these stigmatization things that have been talked about. And maybe those are the two ways in which we can flesh out those terms and give some guidance to IRBs.

DR. MURRAY: Carol will have the last word in this session, except for

Harold.

DR. GREIDER: I just wanted to point out that the first thing that Alta said was that it might be impracticable to drop impracticability. [Laughter.] And the other thing I wanted to say was that I agree with the idea of sending out the draft with this dropping of the impracticability and a cover letter, etc.

DR. MURRAY: Yes, I thought the cover letter idea was an excellent one to point out the things we particularly want people's comments on. Harold, do you have any instructions you want to give us?

DR. SHAPIRO: Yes. Let me just tell you, we're going to take a brief break now. We really do have to keep it to 15 minutes; otherwise there's going to be no possibility of doing the things we absolutely must do this morning. When we return, we will go first of all to look briefly at the rewording, so to speak, of our recommendations we approved yesterday; that is, that memo you have is an attempt to put into language what we approved yesterday not always using very specific language. Jim will go over that and highlight any particular points where there might be some change that wasn't fully discussed yesterday. I want to remind everybody this is not an opportunity to rewrite these recommendations, much as you might like to do so in ways that might please you. This is solely trying to make sure that we haven't seriously misunderstood the issues that were approved yesterday.

I do want to say in that connection that there were three particular issues that came up that are not in the recommendations but will be in the final text, which we will distribute, that I just want to mention so that we don't have to deal with them again later. One is the question of how our recommendations relate to the waiver issue. That we discussed yesterday, and it will be discussed more explicitly in the text. The same thing is true with respect to the regulations regarding children and so on as we discussed yesterday. And, of course, also how these recommendations affect those institutionalized as mentally "infirmed," to use a term of art that has some history. Those will all find their way into text in appropriate spots as indicated yesterday. They do not find their ways directly into our recommendations, as we discussed yesterday.

We will also then move to discuss, I hope I'll have a draft by then, the letter to the President to see how people respond to that. We may be able to finish that this morning; we may not be able to finish that this morning, as I indicated before. In whatever time is left we will return to the Biological Materials Report if for no other reason than to decide what really our next steps are. The discussion has been very helpful this morning and I think we can make some useful next steps.

So it is now almost a quarter after. I'm going to turn to Jim precisely at 10:30. Your absence here indicates that you have no concern about this issue and therefore I will take your proxy. And so 10:30. Thank you very much.

RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY

DR. SHAPIRO: Let me just remind you of the steps. Jim will go over some of the recommendations that we approved yesterday. There are some that need to be changed from what are in the handout that we gave you before, and Jim will get to those, but most of them are as distributed.

But let me say the following regarding what your obligations are if you want to participate further in the finalizing of this report. One is that any textual comments that are outside the recommendations that you would like to see incorporated, examples, editorializing in any other way that you think is appropriate, that has to be in NBAC's offices no later than Monday morning. That's this coming Monday. I'm talking not about the recommendations now but about the changes in the text that you would like to see. And as I said before, we will certainly try very hard to accommodate that.

We will produce on the basis of those comments and those we receive during this meeting a clean text for the commissioners to consider in roughly two weeks. Then commissioners will have an opportunity, having seen a clear text with all the recommendations, etc., to decide if they wish to have any personal comments inserted in the report in cases where they differ in important ways with the recommendations we've approved or something else that you may object to in the report. But you will have really only a week following your receipt of this to submit those comments in writing to the staff, and we will incorporate them as they are submitted. Obviously, those are your comments and will not be altered in any way. And then we will go through the publication process.

So that takes us somewhere deep into December. I haven't made all the calculations, but it's roughly two weeks from Monday that you should receive the report, and three weeks from Monday we should be in receipt of any reaction you have if you wish to contribute anything further to it—again, we're not rewriting the report, I'm just saying if you feel importantly about something you want to be associated with, and then we will proceed to the publication itself.

PROF. CHARO: Question, Harold?

DR. SHAPIRO: Yes?

PROF. CHARO: Obviously, the recommendations and such are all on the public record, but the report is actually made to the President or to OSTP.

DR. SHAPIRO: NSTC.

PROF. CHARO: NSTC, thank you. I would just like to understand better how we describe it if we're asked about it, how free we should feel to write short pieces about the report in the near future if we're asked to by academic or semi-academic journals, etc.

DR. SHAPIRO: I think each commissioner will have to decide that for themselves. I think you can start writing things if you like, but I think we should really try to get the report published. That's not always been observed in this Commission, but I think it is preferable to get the report published. Now if there is some untoward delay, then we can review that issue. But if we can keep on this schedule, that means I'd prefer not to see things published before the report comes out so others have reasonable access to what it is you're talking about. It doesn't feel right to me the other way around. But if there is some unusual delay, then of course we can reconsider this. And I certainly do encourage commissioners to write about it or their reactions to it or whatever else they would like that they think is relevant. I think that informs the public debate and is a very positive thing.

So let me now turn directly to Jim. We are going to take about, we cannot afford a half an hour, that will be the outside maximum we're going to spend on this right now, because we do have to get to the comments on the President's letter and people are leaving at different spots almost minute by minute right now. Jim?

DR. CHILDRESS: After we met yesterday, Harold, Trish, and I spent some time going over what folks had proposed and that Eric and Emily had put down in text. We did discover in the materials that you have one major omission from 19 that Alta has worked on, and you'll be getting a revision in a few minutes or two of the pages or they will be made available overhead. There are three or four where there are wording changes that we need at least to look at and see whether they distort the meaning. We think they clarify the meaning and avoid misunderstandings, but we could be quite wrong about those. So we'll just go through them in order and note where changes have been made from what was discussed yesterday. Number One, no changes.

PROF. BACKLAR: Is it not possible to ask this one question before we start on this, Jim, about the legally authorized representative?

DR. SHAPIRO: We can't spend more than three to five minutes on it. I know it's important, Trish.

PROF. BACKLAR: All I'm asking, actually, Harold, is that we have Jack Schwartz clarify for certain commissioners that I've spoken to. As I understand it, an LAR may be appointed by a person who may become a potential subject, or an LAR may be in a sense imposed upon them by the researchers or someone else. Am I correct, Jack?

MR. SCHWARTZ: The recommendation reflects what I understood to be

the following policy decisions by the Commission. First, a research subject who has the capacity to do so may, and indeed is encouraged to, designate his or her own LAR, and state law should reflect an entitlement to do so. But the recommendation goes on to recognize the fact, if clinical DPA is to be any guide, that relatively few research subjects will in fact designate their own LAR, and the recommendation goes on to answer what happens then if the subject does not designate an LAR. And the recommendation says the answer is to be found in state law, either state law that explicitly addresses research LARs or, in default of that, state law that addresses clinical LARs. That is the recommendation and I believe it reflects the prior decisions of the Commission.

DR. SHAPIRO: Thank you very much. That's very helpful. Thank you.

DR. CHILDRESS: All right, Recommendation 1. No changes were made from what we had talked about. Indeed, none were made, as I recall, during our discussion yesterday.

Recommendation 2, everything is the same until we get to the second page, the sentence beginning "RAPID panel...". That is a reduced version of what appeared on 129, so if you'll glance at that and make sure it represents the Commission's interpretation. It's to get away from the very wordy previous statement.

DR. SHAPIRO: That's the second-to-last paragraph on the second page.

DR. MIIKE: Just a comment: I recommend that we get rid of the word "RAPID." It sort of detracts from the seriousness of it all. We can still call the panel what it is but I would get rid of the word "RAPID."

The second part is that on the guidelines issue, the current guidelines are explicitly tied to the protocol-by-protocol approval. I think the panel should have more leeway; otherwise we're going to get into this delay about transferring responsibility back to the local IRBs. So I would like the Commission to consider that B section about guidelines, eliminating that thing based on protocol-by-protocol.

DR. SHAPIRO: Let me just refer back to the history of this without trying, again, to address this. The history of this was that we had, initially, "promulgating guidelines on the basis of protocol-by-protocol review or the development of new knowledge," or something like that so they could issue guidelines because new information from whatever source was available. There was some concern on the Commission that that was too broad. So I just reflect that. I don't have a strong feeling about it myself. I would be quite happy with adding the words "promulgating guidelines on the basis of protocol-by-protocol review or new knowledge development." But I just want the Commissioners to know. And if we took out "on the basis of protocol-by-protocol," that will of course include any reason that they would have. So let's just see if Commissioners want to restrict this or expand this. What is the sense? Bernie?

DR. LO: I agree with both of Larry's comments. Being more awake today, the RAPID acronym struck me as not being appropriate. And I actually would also agree with deleting from (b) on page 2 the "basis of protocol-by-protocol review." I would give this panel more discretion to base its guidelines on a whole variety of considerations.

DR. SHAPIRO: Let me try to settle it. We talked about this RAPID yesterday after the meeting. The reason we declined to change it was it would mean going into the text and changing lots of other things, because whatever else it may be or not be, it's a very convenient thing to use in the text. So if you will allow us to try to make that decision, we'll see—I don't mind whether we keep it or don't—but depending on how difficult it is to accommodate everywhere in the text, I wouldn't want to throw out that very useful—you may not like "RAPID," but it's a very useful thing to have an acronym to refer back to it. So why don't we just leave that particular thing to see if we can without too much effort change, but I'd like to leave that open.

On the basis of the second one, would it be satisfactory to those of you who want to go broader here to say "promulgating guidelines," as I said before, "on the basis of protocol-by-protocol review or new knowledge that would..."? On knowledge or protocol, do something like that? Alta?

PROF. CHARO: Personally, it's fine. I can't be sure that it's fine to every Commissioner who is not here. A simpler way to do it, actually, would simply be to delete the words "on the basis of protocol-by-protocol review."

DR. MIIKE: Yes.

PROF. CHARO: And in the text, when you finalize it this week, to mention that that along with new knowledge are the two bases that people expect will be used by the panel.

DR. SHAPIRO: Okay, why don't we do that? That's fine. Let's go on. That's a very helpful suggestion. Let's make a note and make sure that that gets added to the text. Very helpful. Thank you, Alta.

DR. CHILDRESS: And so the penultimate paragraph on that page, the one that begins "RAPID panel," I think we can in the text actually be able to use "review panel" and so forth to get away from "RAPID." That's my sense at this point but we'll check it out to make sure that captures in this abbreviated form what we had in the previous one. Any objection to that wording change? Okay.

Recommendation 3 remains the same. In Recommendation 4, and the original appears on page 133 in the text, there were two changes, let me just note: "a description of procedures designed to minimize risk to subjects," and then at the end of the second sentence, "to risk that may be inappropriate." That language replaces "similar

risk."

DR. SHAPIRO: All right. Let's go on.

DR. CHILDRESS: Okay. Recommendation 5, no changes. Recommendation 6, the original is on page 137. Basically there was a feeling when Harold, Trish, and I went through this that the revision that we discussed yesterday and language to make it simpler probably went too far in this sense, that the decision to amend "subjects about their participation may not be overridden by any third party," because we do allow people to remove them from research protocols if they are being harmed. We thought the original language might be better in that regard, which looks more at the beginning of the participation rather than what happens within. That was the reason for that change. We just want to make sure that doesn't distort anything that the Commission agreed to.

PROF. CHARO: Jim, I want to simply say that the acceptance of this recommendation is conditional upon textual language that was offered yesterday. I want to make sure it's still there, to satisfy David Shore, that says that nothing in this recommendation is intended to supplant or overrule Federal regulations that allow for consent waivers under limited circumstances.

DR. CHILDRESS: Right. And that will be in the text.

PROF. CHARO: Right. Because it would appear to be....

DR. CHILDRESS: Thank you for implanting that now, though. Thank you. Anything else on Recommendation 6? Okay: Recommendation 7. Alex had objected to the language of "dissent." Upon further reflection, we thought that actually that probably was a good objection. He dissented to the language of "dissent" so we moved to "objection." We thought "objection" would capture everything without raising the larger question about whether the choice, which was other language being used, was autonomous or not. So that's the change. The other change that's present here is the use of language that [Frances Belet] suggested last week in Baltimore of rather than using "honor" or even "respect" to use the language of "heeded." And so those are the two changes in that particular recommendation. So it's from "dissent" to "objection" and from "respected" to "heeded."

DR. DUMAS: Where are you reading from?

DR. CHILDRESS: This is Recommendation 7. Any objection or dissent or whatever to this particular recommendation?

DR. MURRAY: What's the rationale for replacing "respect" with "heed"?

DR. CHILDRESS: Both "respect" and "honor" we tend to associate

much more with respecting autonomous choices or honoring those.

DR. DUMAS: You might respect them but you might not do anything about it. "Heeded" implies that it's going to be a....

DR. CHILDRESS: We stop whatever we're doing with them is the logic of the point, yes.

DR. MURRAY: I worry that the word "heeded" might suggest the meaning that the people do not have full autonomy.

DR. CHILDRESS: I'm sorry?

DR. MURRAY: I just worry that the concept "heeded" here might actually diminish the respect for the important people who have diminished autonomy. I understand, I think, why the decision was made to introduce "heeded" instead of "respected," but I think it's a diminished form of acknowledgment of our respect for those persons. And I don't see any reason why we shouldn't continue to use the word "respect." I don't have a strong feeling about it. I just think it's less respectful, actually.

DR. CHILDRESS: How about both?

PROF. BACKLAR: Maybe one could say "respected and heeded."

DR. SHAPIRO: I actually far prefer "heeded." I think it's a very simple, straightforward idea: must be listened to, that's what "heeded" means. I think it's straightforward as it stands.

DR. MURRAY: Have a vote.

DR. SHAPIRO: All right. How many members would like to go with the word "heeded"? All right, "heeded" it is.

DR. CHILDRESS: Okay. Anything else about Recommendation 7 here? Recommendation 8 does involve a further attempt by the three of us who were working yesterday to capture what was involved in the discussion. Our attempt may not have succeeded. Please read this very carefully. It tries to build on both things—namely, identifying the independent qualified professional to do the assessment, but then also the protocol would not only describe who would do that but how the individual involved would do that, and then that would constitute one level; and then the IRB could permit investigators to use less formal procedures where the language of the seekers refers to both method and also the independent qualified professional and if there's good reason for doing so. So that was the attempt to capture what we talked about.

PROF. CHARO: Jim, I just want to make sure that in the text it's clear that the choice to use less formal procedures can include the choice to use no particular procedure but just to interact with these particular potential subjects the way you would

with anybody else. For example, I would use bulimia as an example of a mental disorder where there seems to be no reason to assess capacity in any fashion, formal or informal, other than what we do every time a person is a potential subject. And, yes, I will write a sentence for you, Eric, to that point.

DR. MESLIN: Please.

DR. CHILDRESS: For these suggestions, please provide them if you would.

DR. MIIKE: A comment on the same line: perhaps instead of using "less formal," which is a little ambiguous, just say "alternative" procedures.

DR. CHILDRESS: Does everyone agree? Good. Very good. A small one.

DR. MURRAY: On the third line, the sentence beginning "The protocol should describe who will conduct the assessment," that's fine, "and how they propose to conduct it." That's kind of vague. In English, what do we mean by that? Should we say "the nature of that assessment;"

DR. CHILDRESS: That's fine.

MR. HOLTZMAN: Just a quick question, Jim, in terms of the independent. You may have discussed this yesterday. On page 153, in a lengthy footnote, we describe an ongoing assessment procedure that was used in a study and we sort of cite it as a good example. My question is, did it qualify as "independent" in a relevant sense? If we don't have time to talk about this, forget it.

DR. CHILDRESS: We did spend a fair amount of time talking about "independent" yesterday. But it's up to the chair.

MR. HOLTZMAN: That's okay.

DR. SHAPIRO: We'll take a look at it. I don't know.

DR. SCOTT-JONES: On the top of the next page, it says "if there are good reasons for doing so." We had a lot of discussion about saying "only if" and I thought we left "only" in. Was that wrong?

DR. CASSELL: I tried it with it and without it. The meaning is really the same.

DR. SHAPIRO: That's what I think.

DR. SCOTT-JONES: It is?

DR. SHAPIRO: That's what I believe. I'm totally neutral as to whether to put it in or out. It doesn't make any difference.

DR. SCOTT-JONES: It seems the difference is one of emphasis—whether you think it's going to be infrequent or quite frequent that there would be good reasons for doing it.

DR. SHAPIRO: All right, there's some disagreement here. How many of us would like to add the word "only" in here? Diane, I'm sorry.

DR. CHILDRESS: Okay with Recommendation 8, then? We turn to Recommendation 9 and here there is a correction.

DR. COX: I have a point on this thing we just went past. Just reading it, this is Recommendation 8, the second line down, it's really almost superfluous, the entire issue—to permit investigators to use alternative procedures to assess potential subjects' capacity if there's good reason for doing so. What we said up above is all we're asking is to say who is doing it and how they're doing it. I'm just trying to see what the extra content of that sentence is.

DR. MURRAY: But it may not be independent qualified professionals, for example.

DR. CHILDRESS: It may not be necessary.

DR. SCOTT-JONES: I would leave it out, too. I think when it had "only" in it, it tended to convey a different meaning. I think now it would be better to leave it out.

DR. CHILDRESS: Given the vote yesterday and what we have I guess to be cautious about, as the chair reminded us, is not to change the substance, as we did have kind of an approval process yesterday.

DR. COX: So I'm trying not to change the substance.

DR. CHILDRESS: And the question being whether, and this may be a recommendation, as Eric Meslin suggested, maybe go back to "less formal," not the most desirable formulation, but it at least indicates some kind of alternative that's being pursued relative to what was presented in the protocol.

DR. COX: I think we need to leave the sentence in, because otherwise....

DR. LO: I think we need to leave it in.

DR. CHILDRESS: But then I would suggest we just go back to "less formal."

DR. COX: Not ideal.

DR. CHILDRESS: Everyone has a new text at number 9. So if you will look at what you just received, a line had been omitted. So what you have in your

version before you was not correct. But what you have now is correct. Let's see, the term "heeded" is used, but otherwise it's pretty much the same as it was.

DR. DUMAS: The term "as always" seems to me to be superfluous.

DR. CHILDRESS: How do you feel, remove "always"? All in favor of removing "as always"? Okay, looks like it carries. Now we need to move to an overhead because of one omission from this. Oh, I'm sorry, you do have it in your revised version. So look at what you just received, the update, on number 10. The difference from what you had a few minutes ago is that we had omitted (a). Okay. Does this capture everything that we wanted to say in 10? No problem with 10. Okay: Recommendation 11. There were no changes made beyond the addition of number 7. Anything on 11? On Recommendation 12, we need just to look to make sure we got the language right under (d), "is approved on the condition of its approval by the RAPID panel." I think that's the only change there. That was one we've made only one change on. What I was doing on those that we went through yesterday is just pointing to the changes. Anyone want more time or discussion of any part of 12? Recommendation 13 we discussed quite a bit yesterday, and we hope we got the change right: "authorization," on line 2, "to a particular class of research." And everything else remains. We got rid of "no general" and the changes that people had proposed. Yes, Diane?

DR. SCOTT-JONES: I have one change, and this is something that we agreed to do throughout, and that is to use the word "potential" whenever we use "benefits": "potential benefits." Recommendation 13. Line 2, line 3.

DR. CHILDRESS: That's fine.

DR. LO: If we do that, why don't we just say "potential benefits" and leave out the "direct and indirect;"

DR. SCOTT-JONES: Yes, leave out "direct and indirect."

DR. CHILDRESS: And then, just for purposes of this particular one, not worry about "direct and indirect"?

DR. SCOTT-JONES: Right.

DR. MESLIN: So just delete "direct," delete "indirect," and put "potential."

MR. HOLTZMAN: I wouldn't suggest that.

DR. CHILDRESS: In the text we go ahead and talk about all of those.

MR. HOLTZMAN: You could just say "potential direct and indirect benefits."

DR. DUMAS: Well, if you say "potential benefits," that takes in all kinds

of benefits, doesn't it?

MR. HOLTZMAN: Yes, it does, except we go to great lengths elsewhere to make sure that we distinguish for these folks "direct" versus "indirect" so we don't have therapeutic misconceptions.

DR. CHILDRESS: We do emphasize in the text the importance of the distinction.

DR. DUMAS: Okay.

DR. CHILDRESS: So we'll go that direction, if everyone agrees?

DR. DUMAS: Okay.

MR. HOLTZMAN: So "potential direct and indirect benefits."

DR. CHILDRESS: "Potential direct and indirect benefits." Okay, anything else on 13 you want to talk about? Recommendation 14. We made in the first line a parenthetical addition: "within the limits set by the other recommendations," and in (a), "would have chosen" rather than "would have done." I think those are the only changes in 14.

DR. MURRAY: What about the "best interest"?

DR. CHILDRESS: We were talking about it in the text but not in the recommendation.

DR. MURRAY: I thought we decided yesterday to bring it up into the recommendation itself because there will be times when you just won't know what the subject wanted, and to give guidance to LARs about what standard they're to use. That was my recollection.

DR. CHILDRESS: Was someone delegated to provide language for us on that? We never received anything.

DR. MESLIN: No, I don't believe so.

DR. CHILDRESS: We can certainly go back and do that.

DR. MURRAY: I have a clear recollection we agreed that would be included in some notion. The issue is, if you don't have a clear read on what the person would have wanted you to do, then the thing you fall back on is the "best interest." We mention that expressly in the text that explicates this recommendation.

DR. CHILDRESS: One reason there's been a lot of resistance to go in that direction is that we've gone much more than the prospective authorization route here, and that even in cases where the LAR is enrolling someone in research we have stressed the way in which that should be tied to what the person would have wanted.

One risk in going the direction you're going, though one can certainly make the case, perhaps, for some forms of research that involve greater than minimal risk with potential direct benefits, is that when we bring that under the therapeutic model. And so that's where the "best interest" standard would really fit. There's a lot of complicated stuff at work here. I don't have strong feelings about it, but I think if you do work it into the text of the recommendation it will have to be done very, very carefully.

DR. CASSELL: It would be awful hard to do that.

DR. MURRAY: Anyway, I remember the discussion very clearly from yesterday. I made this point. I've given my text over to Eric so I don't have my original text anymore. But in the bottom, in the explication of this recommendation, we say if there isn't a clear indication of the subject's wishes, the prospective subject's wishes, then the LAR may decide based on the judgment of the prospective subject's best interest. We said that. I don't have—fine. But we did say that very clearly.

DR. DUMAS: I don't understand how what you're saying is different from what's in (a) under 14: "The LAR bases the decision...".

DR. MURRAY: That's the so-called "substituted judgment" standard. That is, we try to figure out what the subject, if the person could have spoken for himself or herself, what he or she would have said. But there are some times we don't know that. When we don't know the answer to that, we move to a "best interest" standard. We say that in the material in which we discuss the recommendation. But I'm not going to waste people's time on this.

DR. CHILDRESS: Well, the problem with doing it in 14 in this way is that we have to be very clear about the research to which it's restricted. For example, in greater than minimal risk research, we have worked with prospective authorization where there's no potential direct medical benefit. I would just worry that without a great deal of care on this that we in effect will go back and we'll have some problems with what has been previously accepted as the structure.

DR. MURRAY: This will be inconsistent with the decision we reached yesterday, though.

DR. CHILDRESS: That could well be true on the basis of the discussion yesterday. The question, Harold, is whether we incorporate a "best interest" statement.

DR. SHAPIRO: I understand that, and Tom is right to point out the text where it describes that down below. I thought our decision was that there were more problems with changing it and incorporating it than leaving it.

DR. MURRAY: That may have been the decision in the revising of it. It was not what we decided in the discussions yesterday. But as I said, I'm not going to push it.

DR. CHILDRESS: We didn't have any textual things to work with on this, and so if it was the agreement as approved, it had certainly slipped from our consciousness in working on it because we had no text to work with. So, I don't know.

DR. CASSELL: You can do it by just putting, after the semicolon, "or an estimation of the best interest of the subject."

DR. DUMAS: Well, I thought it wasn't going to be right. I think if this is really unacceptable to the group, then I think we need to change it. But it's okay with me and I don't know how other people feel about it. I'm worried that we are beginning to rewrite the recommendations.

DR. CHILDRESS: Well, Tom is making the point that we agreed on this yesterday. And I'm sorry, I don't have a good recollection of exactly where we ended up on that.

DR. SHAPIRO: Well, let's leave it this way. We will have the transcript of yesterday's meeting before long. If it is agreed to there, we will change it to incorporate it. That seems to be a fair way to do it.

DR. MURRAY: That's fine with me.

DR. SHAPIRO: If it's in the transcript, we'll do it.

DR. CHILDRESS: And we will have to then circulate the set of recommendations to make sure of what is said here, then, and that if we include "best interest" it won't create problems for the other recommendations, some of which are tightly drawn in relation to prospective authorization. Anything else about 14? Okay. On Recommendation 15, which we discussed quite a bit yesterday, we need to determine whether it was a recommendation or guidance. This has been rewritten. Some of us are not happy with "incorporate" but didn't have a good alternative in the second line. But this is an effort to capture the discussion yesterday and then to move us to the point of deciding whether we want to keep it as a recommendation or put it in guidance.

DR. SHAPIRO: Let's just focus on that actual decision. I think this fairly represents what a lot of people were dealing with yesterday. We have two choices. I think it's in the wrong spot in the recommendations, but we need to either keep it as a recommendation—number X or whatever, we don't have to decide that now—or put it in the guidance. I think the people who felt most strongly about this were in favor of keeping it in the recommendations. But I think we just need to decide. We can put it in either section from my perspective. So let's just ask how many members of the Commission would like to keep this as a recommendation in the appropriate spot? Clearly, that's what we're going to do. Thank you.

DR. CHILDRESS: Anything about the wording you want to focus on?

DR. MURRAY: "Incorporate" isn't the right word, but it is hard to think of just what the best word is.

DR. CHILDRESS: We'll leave it open to a good editorial suggestion. If someone can come up on the plane with a....

DR. MURRAY: The other thing would be "rules about medical confidentiality." Should we say "respect for medical confidentiality"?

DR. CHILDRESS: How about "consistent with respect for the subject's autonomy and for medical confidentiality." Is that okay?

DR. MURRAY: Sure.

DR. SCOTT-JONES: And may I suggest "maintain" instead of "incorporate" ongoing communication? That's better, "maintain."

DR. DUMAS: That was the original language.

DR. CHILDRESS: That may have started it, though.

DR. LO: It was the allegation that researchers....

MS. KRAMER: "Establish"?

DR. SHAPIRO: Let's just put it this way. There might be better phrases in here, and if you have them, let us know, and if they don't change the meaning of this we will incorporate them. Because I'm a little bit afraid of doing it here on the fly with so little time.

DR. CHILDRESS: All right, 16 and 17 we went over yesterday. We'll do 16 first. It's exactly, I think, the same as yesterday. Any comments about 16? Okay, now 17 has been—and there should be a comma before "if" in the first line—this has been reworded. We ran it by Jack and this rewording, which seems a little clearer, doesn't distort what he had tried to capture in it. Any concerns about 17? Okay, 18. We revised this, as I recall, in response to direction the Commission had proposed. So we have a much fuller statement about what's involved in the educational materials and their purpose. Any comments here? Anything you want to say, Rhetaugh?

DR. DUMAS: I like it.

DR. CHILDRESS: Okay. Any other comments? We'll turn to 19. Here you need to look at the new one you received, because we had omitted some material inadvertently from that. So turn to the one you just received. We probably haven't proofed it very carefully because the material was added. But if you will look at that and read that carefully to make sure this captures....

DR. MESLIN: The omission was simply moving from the former

Recommendation number 2, the "RAPID panels," and research activities, to this section. That's the addition.

DR. CHILDRESS: And, of course, it had to be reworded when (c) and (d) were brought over.

DR. DUMAS: Looks okay to me.

MR. HOLTZMAN: Why the choice of the word "comprehensive" in the second line?

DR. CASSELL: Change it to "best."

DR. DUMAS: "Best."

DR. CHILDRESS: Any objection to that? Anything else in this recommendation? Steve, were you raising your hand?

MR. HOLTZMAN: No, just reading.

DR. CHILDRESS: Okay.

DR. BRITO: The following sentence is just very wordy; I just thought we could tighten it up.

DR. DUMAS: How is that different from polishing the sentences?

[Tape changed; portion lost.]

PRESIDENT CLINTON'S REQUEST RE: EMBRYONIC STEM CELLS

DR. COX: ... experimentation involved in combining early developmental cells from more than one animal suggests that these new fusions do not have this potential, hence are not embryos. At this time, however, there is insufficient data, insufficient scientific evidence to be able to say whether the fusion of the human cell and animal egg is an embryo in this sense. In our opinion, if this fusion does result in an embryo, important ethical concerns arise, as is the case with all research involving human embryos. These concerns are made more complex by the fact that (UNINTELLIGIBLE). Now, I do want to ask a question to the drafters of this particular part of this. The question is, is the fusion of a human cell, and the question I actually had, can an animal egg result in an embryo? And I want to know from one of you of those who drafted this if that was meant to say a human cell and a nonhuman egg as opposed to just an animal egg. Is that what was meant?

DR. GREIDER: What's the difference?

DR. SHAPIRO: Humans versus animals is the difference.

DR. COX: Humans are animals.

DR. SHAPIRO: Nonhuman was the intention.

DR. COX: The intent was nonhuman animal.

DR. SHAPIRO: Okay. And the result in an embryo, what was the intent? Embryo; human embryo?

DR. GREIDER: Human embryo.

DR. SHAPIRO: Okay, I just wanted...that's what I've got here. I just wanted to make sure I hadn't misread what you said. It then goes on to discuss some issues that I won't read out loud but that are essentially unchanged from what was worked out and deal with the case where—and I'll read the question—if the fusion of a human cell and an animal egg does not result in an embryo with the potential to develop into a child, what ethical or medical or scientific issues remain? It then goes on to discuss these matters, I think in a helpful way, and I should read one paragraph at least because I think it is important: "However, if neither an attempt to create children or the creation of an embryo is involved, we do not believe that totally new issues arise."

DR. CASSELL: Say that again?

DR. SHAPIRO: "However, if neither an attempt to create children"—which is the first condition....

DR. CASSELL: Right.

DR. SHAPIRO: "...or"—we're missing a verb here—"...the creation of an embryo..."—that is the second mission, which is already discussed—

DR. CASSELL: Right.

DR. SHAPIRO: ... so if those are eliminated, "we do not believe," it says here, "that totally new issues arise." Now it had been written as "we do not believe new issues arise." I just changed it slightly to say "totally new issues." Okay. And then it goes on, "We note that scientists routinely conduct noncontroversial research that involves combining materials from human and other species. This research has led to such useful therapies as..."—a lot of interesting examples—"... combining human cells but (UNINTELLIGIBLE) could possibly lead someday to methods to overcome transplant rejections," etc., etc., or to subject women to so on and so on, some examples of where this might lead. There then is a sentence that I do want, and that's really the substance of this. So what I am going to suggest is that I try to complete this letter today, using virtually unchanged what's here, but there might be some other kind of modest

alterations. In view of the, I think, unfortunate impression left by the *Times* article, I in fact may bring up the issue of what we do not believe should be permitted up earlier in the letter just so that people who read the earlier parts see it, so they know that we do have these concerns. And I'm working on that now. I haven't quite got it done.

DR. DUMAS: Did I understand correctly from the discussion yesterday that it is not a preferable approach to mix a species in these types of studies, like human and nonhuman or human and (UNINTELLIGIBLE)?

DR. SHAPIRO: I believe it's true, that David said at one point in the discussion, that those are the hardest experiments and we should do easier ones first.

DR. COX: I said the hardest experiments make it more difficult to interpret the results of the experiments.

DR. DUMAS: I think it's controversial whether scientists would say scientifically it's the best approach or not. I don't think that there would be consensus in that area.

DR. SHAPIRO: So, if that's all right with everyone, I will, if time will allow me to, fax you the letter when I send it to the President, and you'll just have to rely on my judgment. And I will not implicate anybody in the letter.

DR. MIIKE: Just one question, Harold. Are you going to make any reference to the second paragraph of the President's letter to us?

DR. SHAPIRO: Yes, yes. We will respond over the next months to the most important part of the letter, which is the second paragraph. Thank you, that's here. I just didn't mention it.

DR. BRITO: Harold, in reference to your first point, when we did the Cloning Report, one of our primary concerns was the safety issue. Is that what you're referring to in there? And then the fact that that in itself is an ethical issue, and that we can't even begin to approach the potential ethical issues until we deal with that? Is that the way?

DR. SHAPIRO: Yes, but I did not go into detail on that. I have to keep this letter modestly short.

DR. BRITO: No, no, I understand that, but what, when you were—okay.

DR. COX: I am not trying to raise or create new policies here. I really applaud your efforts to have this done very rapidly now because, again, of this unfortunate newspaper article, which gives in my view a very distorted view of what the discussion was yesterday, to have the actual statement in a letter to the President rapidly is very important.

DR. SHAPIRO: All right, Tom?

DR. MURRAY: I want to say for the record that having read this report by Nicholas Wade, who is a reporter for whom I have considerable respect, I think it is a terrible misrepresentation of the concern that many of us have, myself personally included.

THE USE OF HUMAN BIOLOGICAL MATERIALS IN RESEARCH

DR. SHAPIRO: Thank you. Anything else on this? If not, I want to go back, to use what few minutes we have left to decide just what next steps we should take with respect to the Human Biological Materials Report. And since I want to work on this letter, I'm going to turn this over to you, Eric and Tom, to take the last few steps there.

DR. MURRAY: Right. Our numbers are dwindling, and I think they are likely to dwindle further rapidly. Is that a fair assumption? Okay, so let me get your advice then, rather than try to engage in a more substantive deliberation. What's the next step? Now, Kathi, you have certain ideas about when you'd like feedback from us on the report. Why don't you tell us that, and then I want to convey what I thought were some very good observations by Mark Sobel about our request for turnaround for public comment. Kathi, tell us when you'd like to hear from us.

DR. HANNA: Tomorrow. No, actually, as soon as you can get your comments to me the better. At some point we're going to just have to stop the discussion and get the report out for public comment. If you can get comments on Chapters 1 through 5 back to me by no later than Wednesday of next week, that would be most useful. If things come in after that, we will do our best to accommodate them.

DR. MURRAY: When are we going to try to post a draft of this?

DR. HANNA: We would like to get this ready to go out for public comment by December 1st.

DR. MURRAY: All right, so next Wednesday is the Wednesday before the Thanksgiving holiday, and December 1st, I think, is the following Tuesday. Will that be enough time?

DR. HANNA: Yes.

DR. MURRAY: You're planning not to have a Thanksgiving holiday, is that it?

DR. HANNA: No, I just know from the patterns of this Commission that

I'm not going to be inundated with a lot of comments by next Wednesday.

DR. GREIDER: You may be surprised.

DR. MURRAY: Eric has asked me to ask the commissioners the following question: is it reasonable at this point to say that whatever we put on the Web in early December, and we'll try to do it by the 1st, could properly be labeled a Commission draft? Should we vote on that? Let's vote on that. All those who think it should at this point be labeled a Commission draft, please raise your hands. All those opposed to doing that at this point, please raise your hands. We have no objections on the record to that.

MR. HOLTZMAN: Will you respect or heed that?

DR. MURRAY: Someone please remove Mr. Holtzman from the room. Mark Sobel's comment was this: if we permit 45 days for commentary and public response to what we post, and we post on or around December 1st, that's a very busy and distracted time of year for many people. It could be difficult for professional groups, for example, to organize and get comments to us in 45 days, which would be roughly January 15. So do we want....

DR. MESLIN: When's our next meeting?

MS. KRAMER: January—it's the 16th or 17th.

DR. MESLIN: 19, 20? After the 15th.

DR. MURRAY: Okay, the next meeting, I'm hearing, is about the 19th or 20th of January. My concern is, Kathi, that between the 15th and the 19th is probably not sufficient time to incorporate all the public responses.

DR. HANNA: Well, the process is as public comments come in, staff process them and try to collate and present them in a way that's useful. So that's an ongoing process. Certainly there are two considerations. One is that we are trying to avoid the practice of discussing and meeting on a report that is out for public comment, just because procedurally it gets complicated for those who are commenting when they feel that the draft is still being revised. It would be nice to have most of the public comments in by the time you have your next meeting. We can present to you, if only in a verbal format, the nature of the public comments. Some of them you will actually be able to see in a collated fashion. The second set of issues has to do with just the mechanics of staffing, which is that we need to schedule. We now have a new report that we have to contend with on top of the other reports that we haven't discussed today, which are the Comprehensive Report and the International Report, and I'll let Eric talk about the staffing issue. But we really need to get the HBM Report progressing rapidly.

DR. SHAPIRO: I think 45 days is more than enough time, and I

understand it's an unusual period, but nevertheless I think it's more than enough time. And in any case, it's the time we have. And so we ought to just make it happen in that time.

MR. HOLTZMAN: Is there a formal way we can get out to the professional societies tomorrow that we will be posting this on thus and such a day, so that they can put in place whatever is their process?

DR. MURRAY: The comment by Eric is, we'll do our best. Please, most members of professional associations who are here, interested associations, please notify your respective organizations that we will be posting it by, we hope, December 1st. We would hope to get your comments by January 15. That doesn't mean that you can't continue to give us comments, but we would very much like to have whatever you can do available to staff as early as possible so that we can consider it during the meeting in January. I think we should simply heed our chair's advice about this.

DR. SHAPIRO: Are there any other issues about compiling or process for the Human Biological Materials Report that commissioners wish to raise at this time?

DR. HANNA: That's what I said....

DR. SHAPIRO: Okay, David?

DR. COX: I would just like a clarification. Kathi had three questions for us, and when we leave here today I'd just like to know what our conclusions were concerning those three questions.

DR. MURRAY: Yes, no, maybe, and on alternate Thursdays, those were the answers. No—Kathi, what was your understanding of the answers?

DR. HANNA: My understanding is that for question number one, we will take up Dr. Shapiro's suggestion, which is that in the recommendations when we refer to what we are now calling "unidentifiable" we make it clear that we're talking about "unidentified" and "unlinked"; even though we are treating those the same, we will keep the distinction in the text so that investigators understand that within this category that's being treated the same way there are subcategories that might deserve special attention in the way they design a study or whatever. That's one. Number two is, I think I have a sense from the Commission that the big picture is that you see this research by and large as about minimal risk; however, there are significant types of research in this area that are above minimal risk, and we need to focus more specifically on what we're saying about those. So that just really is trying to reconceptualize the way that the report is introduced and the recommendations are introduced. On the third, we're going to go ahead and test the waiver or the dropping of the practicability requirement. We're just going to put that in the draft—and the opt-out—and see how public comment responds. And then on the fourth, having to do with saying more about future consents, staff will

try to work with commissioners who have indicated that they would like to help. Dr. Lo indicated he would like us to think through that a bit with him. So the only thing we didn't address in there was my question about redefining what we call consent in the clinical context, and if you want to just respond to me by e-mail or whatever, it's not a significant issue. I don't think we need to take up any time on it.

DR. MURRAY: If there are no other specific clarifications or comments about the process and timing of the Human Biological Materials Report, I'd like to turn it over to Eric Meslin.

DR. MESLIN: For those who are keeping track of the agenda, I just wanted to mention for the record that there were two items we did not have an opportunity to discuss at this meeting. The first was the Comprehensive Human Subjects Project, for which an update was going to be provided. We will circulate materials to the Commission on that; you already have some from discussions with Kathi and Alta. Second, and with some regret, I did want to report—the report is I didn't have enough time to do it—report on two activities on the international side of our work. One was a very successful meeting that was held in Tokyo when Dr. Shapiro and his colleagues Jean-Pierre Charchew (phonetic) and Hiro Imura (phonetic), the respective chairs of the French and Japanese National Bioethics Commissions, cochaired the single largest collection of National Bioethics Commissions in history in Tokyo for two days. It was a very successful meeting, with membership from our Commission represented by Alex Capron, Tom Murray, and Alta Charo. The resulting product of that second international summit of National Bioethics Commissions was a two-page communiqué that is now in the process of obtaining final signatures. There are 35 signatures from National Bioethics Commissions and seven international agencies that pledge continuing commitment to work together to look at international issues, to share resources, to work together, and to develop further research opportunities. And I think that's in no small part due to the leadership of Dr. Shapiro and his colleagues in France and Japan, as well as to the tireless work of Alex Capron, who isn't here today but who worked extremely hard in helping to convene that meeting and to prepare the communiqué. We will circulate it to all commissioners because it is a very nice document. And second, just to report very briefly, we have now under way, despite the fact that our research agenda is rather fungible at this point and moving in different directions, continuing our work on the international project with three Commission activities looking at empirical work both here and abroad. I won't take up all of your time now, but we'll send materials around to commissioners, both by e-mail and hard copy, and it will be available to the public if they so desire, which describes the work in progress. I'm hoping that at our January meeting, then, there will be a more full discussion of the progress that we're making on the International Report.

DR. SHAPIRO: Thank you very much. Any other business to come before the.... Bernie?

DR. LO: I think this is sort of a good opportunity for us to pause and take a big deep breath. I mean we've got our second report almost out the door; we've made, I think, good progress on the Biological Materials Report, and we've gotten this big, new assignment. And I guess I'd like to think through a couple of issues: one, given the importance and the short time course of the President's request, how are we going to set priorities to make it realistic for the staff and everybody? And then second, could we reflect a little bit on how we've worked on these two reports? I understand it's very tough doing two reports at once, but in looking back I think a lot of us are frustrated that we somehow took this long to get to where we are. And if we're going to be entering a phase of having potentially three new projects getting off the ground while we're finishing the Human Biological Materials one, can we think a little bit about how we can make our deliberations more productive? On the one hand, I think sometimes—like perhaps this morning with the Human Biological Materials—we seem to get a lot done and really make progress. And at other times I think there's a sense that we're going back to issues that we had talked about before and going in circles. And given what we're asking ourselves to do, it might be a good time for us to reflect a bit on how we can do our job even better.

DR. SHAPIRO: I think that is always an appropriate thing to do, and maybe an especially appropriate moment now. I want to make a couple of comments. I don't think we can easily carry on that discussion today, we don't have time, but I think it's a very important discussion to have. And so I appreciate you raising it. First, it will not be possible for us to proceed on anything like this agenda if we don't have a new understanding regarding the resources available to the Commission. That's just not going to be possible any other way. And that's something we're going to have to talk about and report back to the Commission about it. A second issue is not only how we organize our meetings and our staff and so on, but how responsive the commissioners are to requests that we send out. Now the frank truth is that sometimes we hear nothing, sometimes we hear a lot, sometimes it's all up and down. And we're going to have to ask ourselves, those of us who are members of the Commission, how much, given the fact that all of us have so many different commitments, whether it's realistic to give the commitment that's necessary to get this going at a faster pace. And other staffing issues also need to be addressed. So I'm very appreciative and embrace the issue. We should have at our next meeting some time to discuss explicitly these issues, and by that time we'll have more information. Other issues to come before the Commission? Once again, excuse me, Bette.

MS. KRAMER: I want to thank, on behalf of all the commissioners, I'm sure, thank Arturo for the arrangements for this meeting. It's going to be hard to go back to Crystal City.

DR. SHAPIRO: That's right, it'll be hard to go back to our normal venues. We may never go back; you'll never see us again.

DR. MURRAY: It's no Cleveland, but it's nice.

DR. SHAPIRO: Where is the Rock and Roll Hall of Fame, anyhow? But anyway, thank you, Arturo, very much. I'm very glad to have been here. Enjoyable for all of us. We are adjourned. Thank you.