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**Continued Discussion of the Staff Draft on Research Involving Persons with Mental Disorders Affecting Decisionmaking Capacity: James F. Childress, Ph.D., Jonathan Moreno, Ph.D., and Commissioners**

DR. CHILDRESS: We had discussed all of the topics on page 2 down to referent population for risk assessment.” So, why don’t we start there, and then we have a few more on the next page, as well as Laurie Flynn’s concern about the necessity requirement, and there may be some other points left over as well that I did not note. So, let’s start with the discussion of the referent population for risk assessment. This appears on pages 99 and 100. If you’ll glance at those pages, unless you recall them well from an earlier reading, we’ll see if we can handle this particular topic fairly quickly.

Jonathan or Eric, is there anything you want to sift over? Oh, Alta, go ahead.

PROF. CHARO: Consistent with where we were yesterday, I think the simplest thing might be to use the same definition of minimal risk and referent population as is used in the Federal regulations; specifically, the general population is an average of sick people and well people, and that there be a reminder in whatever document we ultimately send to the IRBs that reminds them they are always welcomed and encouraged to look at the specific population in the study and ask would ordinary minimal risk items be of more than minimal risk for them in particular and to adjust their protections accordingly, but not to try to change the definition of minimal risk for the referent population just for this purpose.

PROF. CAPRON: Alta, I think I agree with the objective but I disagree with the description. Taking into account what’s going to be done in the research and then figuring out what risk that represents for the population is not a matter of altering or departing from the notion that the definition of minimal risk is in reference to the whole population. It’s two different issues. One is, what is that level of risk? Obviously, what one is doing is something that doesn’t yield a number, it yields a lot of analogies; walking over here from the hotel has a one-in-a- million chance of sudden death or something. That’s the risk of ordinary life. As frequently as I go to see the doctor in a year. I mean, these kinds of things.

Whether going into a PET scan is more risky for me or more risky for one of the people who is actually going to be researched isn’t really relevant unless going into a PET scan is not one of those base line things. One does have to ask, what is the risk for the population compared to what? And the “compared to what” are the minimal level of risk encountered in ordinary life of the general population, including the well and the ill.

PROF. CHARO: I take your point. But I’m thinking more at the level of the routinization of these kinds of recommendations. Now, on my IRB, if something involves something like a venipuncture which is ordinarily considered minimal risk for typical study populations, it means that the IRB administrator assigns the protocol differently. The protocol is not distributed to everybody, only to the reviewers who report back in the meeting instead of having everybody read it, right? And so, for example, if I were the assigned reviewer, I might be one of only two people reading the entire protocol. And it would be the job of the IRB administrator to either determine that, based on this subject population, maybe we shouldn’t treat it this way, or me, as the reviewer, to bring to the attention of the committee that maybe we shouldn’t treat it this way.

But to ask the IRB administrator to apply a different standard to begin with in figuring out how to routinely manage the review of these things is what I would like to avoid. That, I think, is just an invitation for confusion. And to simply say we're not going to deviate from the Federal regs, but to point out to IRBs they need to pay attention to the population, which is what I thought I said, accommodates this requirement that people will take into account who it is who's being studied.

PROF. CAPRON: The phrase "they are always free to adjust" made me think you were addressing the metric, where is the bar, not where does this particular procedure —

PROF. CHARO: No, no, no. It's this particular procedure when they review this particular protocol.

DR. SHAPIRO: I think you're both saying the same thing here. I want to ask a question on this, if I may, Jim. And that is, I think I raised it yesterday toward the end of the afternoon, whether we would want to caution the IRBs that after taking all these special considerations into account, they can never exceed the referent bar just because it's this group. That is, they can't talk themselves into going past this reference by ascribing special characteristics.

PROF. CHARO: In other words, they can't wind up putting these people at more risk because typically they have more medical interactions, et cetera.

DR. SHAPIRO: Correct. That's right.

PROF. CHARO: And this is a classic thing that happens not only with these people, cancer patients routinely have more interventions, et cetera.

DR. CHILDRESS: Okay. Thank you. Do we need further discussion of this particular topic? Are we satisfied?

DR. MESLIN: I don't want to hold the proceedings, but we did hear in written form from Laurie Flynn and I don't want to quickly leave the subject in the event that we want to make sure that we at least attended to some of the points that she's raised, which we did discuss yesterday. And I'm hoping that Alta and Alex's agreement, so to speak, the description of what we think we're saying, can be read in the spirit of some of the concerns that Laurie had.

Were she here, she would probably say them herself, but one of the worries that came up yesterday was if we go this route, will we be preventing research from going forward? Will we be limiting certain types of research?

PROF. CAPRON: And that was to be a question to the public, can you give us examples?

DR. MESLIN: Okay. I just wanted to bring us back.

PROF. CAPRON: You may want to see if there is a division of the house on this issue, because I gather Laurie is not alone in her view that we should have a different approach for that intermediate category, which does not lead to bottom points.

DR. CHILDRESS: That's my sense in talking to individuals as well, that there would be some division.

PROF. CAPRON: And I don't think that's going to be affected by the description either.

DR. SHAPIRO: No, I don't think so.

PROF. CAPRON: The question is, should you be prepared for a statement at this point that the following Commissioners believe that the correct approach should be something else?

DR. SHAPIRO: Why don't we just see? I don't want to take a long time this morning. Clearly, I think we're going to have some disagreement on this and there will be certainly opportunities for Commissioners to express their disagreement within the report, if they feel strongly about it. But let me just ask that question, this is what I call the two- versus-three categories problem; that is, whether we're going to have the minor increment over minimal risk receive less protection than whatever is on the other side of that bar?

MS. KRAMER: Harold, have we given up on trying to accommodate Laurie's concerns other than having that category of three? Is there any other way that we could formulate

DR. SHAPIRO: Laurie would have to speak for herself, but I think from what she's written it seems to me pretty clear that she and I are in different spots here and I don't know where the rest of the Commission is. We'll have to see. She may change her mind or not, I just don't know.

Steve?

MR. HOLTZMAN: I think I'm in Laurie's camp but not necessarily requiring three different categories. Because from my reading of Laurie, the real issue if you go to our flow diagram, is where you go down to in light of the specific study population, does this research involve greater than minimal risk. And that in the case of the — yes, there is one pathway in which the research can't be done at all. Right?

PROF. CHARO: Yes. If it's non-therapeutic and they can't give informed consent.

PROF. CAPRON: Secretarial approval.

PROF. CHARO: Right. Yes. But that's realistically that's not much of an out.

MR. HOLTZMAN: That's exactly right. So that if there was a pathway opened up to leave that research to be done, we need not have the third intermediary category. I read Laurie as creating that category so that there's a pathway for that research to be done.

PROF. CAPRON: But I read Laurie as saying that she would agree that greater than minimal increment over minimal, greater than minor increment, is appropriate. So you don't fix that category by saying, well, we don't need secretarial review, we need OPRR review or division chief review or something.

DR. SHAPIRO: Bette?

MS. KRAMER: I would like to request the staff or whoever to try to find a way to incorporate Laurie's concerns within this flow diagram. I think that there's nobody on the Commission whose life is so completely devoted to the protection of these people as Laurie is. And I, myself, would be loathe to sign off on any document that didn't incorporate a concern about which she feels so strongly.

DR. SHAPIRO: Well, Eric?

DR. CASSELL: I think there's another way out of this, actually. When we make it three categories of risk like that, we get into what's in that category. Right? But if we say that over, instead of having that category, when a protocol suggests this risk-taking procedure, spinal tap would be an example, or the one she's concerned about, or certain kinds of PET scans, it ought to be so specified and acted on as that thing by the IRB; specifically, in this instance, with the protections that are in place for these patients, is that a permissible thing for them to do. So that we don't just open up the bag, but made it specific risk-by-risk thing.

And if, in fact, the IRB thinks that it is too risky for this population, then it goes on. But if they see, a spinal tap is a good example, that this is a population that has in the past had spinal taps and so forth, then that might be permissible. So we're not making it open-ended anything in that group you can do, we're making it risk-specific.

PROF. CHARO: I'd like on this particular occasion to argue for a line in the sand. And I recognize exactly how difficult this is because this is exactly the issue on which this area of policy has floundered for 20 years. It's about the very fundamental tension between protecting these people against the exploitation that we have seen happening for years and their inability to protect themselves as well as we would like them to be able to versus the fear of lost research in a population that wants very much the best advances.

You can't quantify an instinct, and, therefore, I can't be sure I'm right. I've only been serving on IRBs for a decade or so, but my impression from that decade is that there is never any lack of pressure to expand the boundaries of permissible research. That the dominant pressure is always to get more research done. That one has to erect bulwarks against that because it is extremely easy in the context of a particular protocol, as you were suggesting, to find reasons why you want to go ahead and permit it and, in an incremental way, to find yourselves at the end of the day in a situation in which basic civil rights or human rights in fact are being violated. And we've seen it happen over and over.

I don't think human rights and civil rights can ever be achieved in a way that is efficient, nor do I think they can be achieved in a way that does not have some real cost to societal advances. We accept those costs because we think it's so important to in fact create this bulwark against exploitation. So this is based entirely on an instinct of protectionism from my observations. And I can't argue with people that I'm right, I can only report my observations from those reviews.

And for this reason, I still fundamentally disagree with Laurie. And I respect her

involvement. I also respect the fact that we could have easily had somebody who takes exactly the opposite position in terms of protection of human subjects with an equally illustrious CV with regard to involvement in this area sitting on the Commission and then we would have watched them fight it out. And so I don't —

DR. SHAPIRO: Let me say a few things about this because I think we do have to move on today. We can't resolve this whole thing here. One, I think it's fair to say that nobody on the Commission has any special status over anybody else in the Commission. We all have our judgments and there's nobody on the Commission on any issue for whom we should defer, although we should respect all views on this.

Second of all, just speaking about this issue, I'm unconvinced myself either by the logic of the argument for three categories or the empirical statements that are made that this is going to have this and that effect. Now, there may be some data that would convince me, I'm open to it, but I'm really unconvinced. I think what we have here right now is a disagreement, and it's an understandable disagreement, reasonable people can disagree on this issue, and so I think for the purposes of moving ahead right now, we can just move ahead, we will flag this issue, we'll have to decide how we all come down on it and —

MS. BACKLAR: I can say something? Hello. Yes. Harold, I'm very pleased to hear you say this because I really can't follow the argument because I can't hear most of it. But it is something that I am concerned about and I take the position that I know it is not aligned with Laurie's. And, therefore, as both of us are out of this discussion, I would hope that you would let us have a little more time where both of us can be involved in some way also. Because I don't have Laurie's paper in front of me and I certainly don't know what her arguments would be. I do know what her position is, and I just want to make it quite clear that I believe that it is better not to have three categories but only to have two.

DR. SHAPIRO: Thank you. Larry, and then I'm going to make an executive decision to move on here.

DR. MIKE: A couple points on Laurie's paper. I guess if we drew the line at "minor incremental over minimal risk" rather than at "minimal risk," I wouldn't see much difference anyway and we would be arguing about some very specific things. So I'm for two categories.

She does raise a last one, which is this issue about excluding people altogether, except her example doesn't seem to match because she's saying therapeutic research. To me, therapeutic research means that person is qualified. So I don't understand that. I see her raising the issue but the example that she uses doesn't support the argument.

DR. SHAPIRO: Well, look, we're going to make a draft, we're going to flag this issue for people to get feedback on and Commissioners can think carefully about where they're going to come out on this because I think we may very well end up disagreeing, and if we do, we do and we'll just generate a report which flags that disagreement for others to decide eventually.

Steve, and then we'll go on.

MR. HOLTZMAN: Procedural question. I think what you said was we don't have a good sense of how much research, what types of research might not be allowed to occur.

DR. SHAPIRO: That I don't have, correct.

MR. HOLTZMAN: Right. And I don't have it either. It's a question I asked yesterday. If one is going to throw out bath water, one ought to know just how many babies and how large they are might be in there. And I think that's a function of what is the research that's likely to occur and what is going to be the interpretation of minimal risk. And I think we cannot—or I don't feel like I can decide this unless I can put my arms around that.

DR. SHAPIRO: That's fine. I don't know whether we're going to be able to provide adequate data. You may not be able to get your arms around it, therefore. Therefore, I don't know where that will take you.

My own view as I've looked at these things, you're left with those issues no matter what you decide. Whether you're three or two, you still don't know where you are because I can't get people to fill in these boxes. But we'll give it a try. Yes, Bette?

MS. KRAMER: Would it be possible when we put this out on the web or when we solicit public comment to flag this issue and say that the Commission had certain questions about this particular issue?

DR. SHAPIRO: Yes. That's the intent.

DR. MESLIN: In fact, if Commissioners want to identify the very individuals or groups who they feel are best qualified to respond to this question, staff would be delighted to receive those suggestions so that we can direct the report to those individuals on this issue.

DR. SHAPIRO: Jim, I apologize. We'll go on to the next aspect of this.

DR. CHILDRESS: I guess my sense is that finally however much data we get in this area, we are going to be left with a fundamental philosophical difference at this point whichever categories we use, as the Chair indicated, and that finally we'll have to vote and there will be perhaps a majority statement and a minority statement.

On IRB membership, the next topic, we saw a recommendation from the NIH Expert Panel report yesterday, which called for one representative. We've recommended two subject representatives, and we've recommended this as a matter of regulation that such change should occur.

The question being raised here is whether we agree with the recommendation as it stands in the draft report, and whether we offer sufficient reason for that. The relevant pages are 169–170, and 150–155 in the document.

Is there discussion of this particular topic?

DR. SHAPIRO: Anybody have any concerns?

On the smaller issue, Jim, there's a second question here, is the justification provided.

There actually is an interesting justification, but it occurs elsewhere in the report when we're on to some other issue. I can't put my finger on the page right now, but there's a spot in the report—you may know Jonathan—where you talk about the fact that training in this area is not widespread even for physicians and so on. There's some conversation about that early on in the report dealing not with this point, but it's directly relevant to this point. I'm sorry I can't give you the page reference, but you may try to just bring that forward again when you look at this particular recommendation.

DR. CHILDRESS: Okay. No discussion? All right. Let's turn to the dissent standard. We have in the report still the apparent dissent standard and it's discussed in several places, 116 and following, 157-58, 178. The question here, and we talked about this briefly at earlier meetings, is whether we want to retain the apparent dissent standard.

Is there discussion of this?

DR. SHAPIRO: Remember Jim's rule from yesterday, that is, silence means you're all right with what's here.

DR. CASSELL: Or you can't find the page, one or the other.

DR. SHAPIRO: That's only for older people like you and me, Eric.

DR. CASSELL: You gave the wrong page reference for that. Sorry.

DR. CHILDRESS: I gave you the right pages, 116 and following, 157-58, 178, and there may be others but at least those deal with it.

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

DR. CHILDRESS: Anticipatory planning. We discussed this around 120 and following, and 163. This is also a topic that was discussed at considerable length in previous meetings. The question is whether the way it's now handled in the draft captures the kinds of concerns that people have raised earlier and whether what we have is now sufficient.

DR. CASSELL: What page? That is the pages listed or —

DR. CHILDRESS: Those pages are accurate, right.

Then we have the additional recommendations listed below that I guess grew out of Commissioners talking with staff as possible additional points. These have not really been discussed very thoroughly. Some have been touched on in passing. So let's start with the assessment of prospects for loss of decisionmaking capacity. You see the statement here, and the question being raised is, is this a direction the commission would like to go?

Eric, do you want to comment?

DR. MESLIN: We talked about this yesterday with the second flowchart. The question was whether or not in addition to any assessment of capacity that is done as an entry point for recruitment, should there be built into our recommendations any additional assessment of capacity for those individuals who might prospectively lose it during the course of their participation in a

study. We have not built that into the flowchart. We've been working with various ways to do that. But given the subject population and those for whom this is appropriate, we felt it was necessary to raise it for you. There isn't language for you to comment on, so it may need to just be discussed for a minute or so.

DR. CASSELL: Just so I understand what the topic is leading into what you have here. There are, in fact, persons who have the ability to consent at point A, but later on in the project they may lose their ability to comment correctly or lose their capacity, and we have no mention of that. We don't discuss that?

DR. MORENO: Well, in a way we do, because we do have this notion of anticipatory planning. The problem is—if you see it as a problem—that there's no device to sort of goose people to focus specifically on the problem of prospective loss of capacity, though one would hope that that would be part of the anticipatory planning process.

DR. SCOTT-JONES: I was just going to say that on page 163, I read that to mean what is listed here, it refers to the prospect of a loss of decisionmaking capacity during the study period. So what are you saying that's different?

DR. MESLIN: First of all, we haven't decided about anticipatory planning. If we are comfortable with the protections that that provides, then this may be unnecessary. But the difference is if an individual has identified their preferences for a future time, we're only asking whether there should be a mechanism that kicks in to determine whether or not they are fully capable, or, in fact, whether that anticipatory planning does, in fact, kick in, because it would only kick in if the individual is incapable. If they are capable, then one doesn't refer to their anticipatory planning preferences. So they are connected.

DR. CASSELL: It's not unusual—let me go back a step. Many of these projects go on for a number of years. It's not unusual during the course of a project for something to be added to the project using the same population because of what's transpired. By that time or at that time, one of the subjects may no longer have the ability to consent.

As far as I'm concerned, when that happens, that person should be protected as though they hadn't gotten that ability from the beginning. Anticipatory planning may not solve that because they won't know what is coming on the board, that's number one. Number two, if they have family protecting them along the line, then we've already got this covered. In other words, I don't think we can act as though once somebody has consented, that's it, there in. It's like going over Niagara Falls, once you get in the barrel, that's it, you're on your way.

DR. CHILDRESS: Further discussion?

Alta?

PROF. CHARO: You know, it occurs to me that good research, and you're right about twigging people to do this, good research, when they first recruit people, would include this in the discussion. It's going to become an issue only when we're contemplating a change of the

person's status; for example, they're participating and they now need or want or would have wanted to withdraw, or they weren't participating and now they suddenly want to be in. That's the kind of thing that when done properly would, in fact, happen at the time of the early enrollment. Because with this population, one of the things that will happen in that discussion ideally between the recruiter and the subject is, what do you want us to do if you get foggy during the course of this research? Do you want us to pull you out immediately, or do you want to have somebody else making decisions for you, or do you want to give us rules now to follow?

And you're quite right that you might want to just flag that with this particular population, since this is such a high probability occurrence, that good recruitment practices would include some discussion to flag this for the subject.

DR. MORENO: Can I just add that, if this flow of conversation is finished, there's another angle on this question that we also discussed and also comes out of this formulation. Many people would argue, and Laurie might be one of them, that there are lots of folks who have mental disorders who are not at high risk of loss of decisionmaking capacity and that it's unnecessary to invoke the apparatus that we're recommending in this report for people like that. And for want of a good example, I'll just think of sort of garden variety Upper West Side-style neurotics of whom I know more than one, some —

DR. SHAPIRO: That's a New York job.

DR. MORENO: Some of them are our colleagues.

PROF. CHARO: Some of them are sitting at this table.

DR. MORENO: Right. Or from Brooklyn, I think that counts also. People whom you might say have a mental disorder but are not at risk of loss of decisionmaking capacity. And you might well want to study those folks if you work at Columbia and yet you see this very complex apparatus before you that seems irrelevant.

Now, this is a big question that I sort of want to put on the table at this point because it is a suggestion that's come up in my conversations with various people in the last few weeks when I've shown them the draft and the chart that you're all struggling to interpret. They say, this makes sense for many people, it doesn't make sense for a lot of people who could be construed as having mental disorders because they're really not, however you want to put it, at significant risk, substantial risk of loss of capacity.

This is perhaps another question that we might want to flag for the Web and I'll just put it on the table at this point.

DR. CHILDRESS: Larry, and then Eric.

DR. MIKE: But how in practice would one differentiate? It seems to me you would have to set up a protocol before the protocol to decide which people are in or out.

MS. BACKLAR: I can't hear what you want to flag. So I hope that somebody will

E-mail me something about this.

DR. SHAPIRO: We will do so.

DR. CASSELL: Well, the number of disorders that have as part of them the loss of decisionmaking capacity is not endless and they do not constitute most of the people walking on both sides of Broadway. It's the ones sitting on the bench in the middle, and they have diagnoses. We're not talking about just ordinary neurotics, we're talking about people whose mentation or cognition becomes impaired by their disease. That's not an endless list of people. Also, those are the people who may, in the course of their disease, become impaired or become no longer impaired.

I think you can't act as though all of this happens at one point in time and then it's over. So that we have to have some mechanism of protecting somebody whose decisional capacity changes.

DR. SHAPIRO: It also seems to me that the apparatus is not cumbersome for that very population. Decisions can be made quickly and it's just not cumbersome for that population compared to the risks one would take on in trying to make two different sets and say one of you falls in this box, one another box. That's much harder it seems to me and maybe just as cumbersome.

DR. CHILDRESS: Diane, then Alta, and then Alex.

DR. SCOTT-JONES: I just wanted to be sure what the question is that we're addressing. Are we saying that we should somehow decide which categories of persons should not be subject to this because they're not at risk for becoming incapacitated during the course of a study? I'm not sure what we're addressing that's different from what's already in the draft on page 163.

DR. CHILDRESS: Eric, could you comment?

DR. MORENO: This notion I guess rests on the theory that one could assess a whole population rather than individuals. So let's say the whole population of garden-variety Upper West Side neurotics, we'd say, don't require the protections in this system, rather than individuals. Then we'd do a population-based assessment and we'd convince the IRB that that is the case and that's valid. And then they would be treated like any other subject.

PROF. CHARO: I think that the structure of the interactions here may solve this for us, even if intellectually the problem is as you state. Look, I'm a researcher, I want to keep my subjects who have enrolled in my protocol so that I can finish out my study. That means that if I look at somebody and I think this person is at substantial risk of losing their ability to continue to be consenting and voluntarily participating, I'm going to have an incentive to have a conversation with them about some kind of advanced planning because if I don't do that and they do lose their ability to make decisions in the course of the study, I'm going to have to drop them out. You can't keep people enrolled when they're no longer capable of making a continuing personal decision to stay enrolled.

So as a PI, I'm going to have an incentive to aggressively seek out those who need this and to talk to them about it. And that may solve the problem without us having to have anything

analytically down here.

DR. CHILDRESS: Alex, and then Eric.

PROF. CAPRON: I think Alta is correct that the question only arises as there is some decision point that one would reach. But I don't think, Alta, that it will necessarily be self-policing by the investigator. Because if we look on the chart, I think what we're talking about is the box that begins with the word "approved," a box which I don't understand the way these two clauses or sentence or whatever it is go together. But it's at that point where we're saying during the course, if it's a week long or month long or whatever study, and during the course of it a person with fluctuating capacity moves from capable to incapable, they might move, for example, if we were over on the left of those two identical boxes, to say yes, they were but not, no, they are not any longer capable of giving consent, so we need to notify them that we've reached that conclusion, and then turn to their legal representative for the permission to take the next step in the study. And if they don't start kicking and screaming — the real issue will arise when the person starts saying, "I don't want you to do this anymore." And the question is, is this a crazy person's reaction now that we disregard? And that's why these fulcrums of "are you capable or not" is so important. And if it's minimal risk and it has some benefit for the person, the legal representative would be able to say, no, keep them in the study.

You've determined they're not competent. I'm going to disregard that unless we say the no apparent dissent rule applies. And if they're dissenting, then knock them out on that basis and it doesn't matter. But in that case, the advanced planning isn't going to help. It's not as though I'm going to pull a certificate out and say you signed the certificate before saying you wanted to be in this, this is a Ulysses contract and we're going to disregard your present dissent.

DR. CHILDRESS: Alta, do you want to respond, and then Eric?

PROF. CHARO: We did agree that the no apparent dissent standard is going to be the one we're with for the moment, correct?

DR. CHILDRESS: Yes.

PROF. CHARO: So the situation we're in now is only one where somebody's continuing capacity to consent appears to have diminished and they're neither dissenting nor assenting, they are simply continuing to be used in the study. And the only question is whether or not there is a mechanism to identify that moment and perhaps invoke some other set of protections. I would hope that at the time that the protocol is originally reviewed by the IRB that the subject population is being looked at, and if it is a population in which you have the kind of fluctuating capacity you've described, that the IRB's in fact in a position at that point to be thinking about this with the PI together. We know that it can't be made totally perfect without having monitors necessarily attached to everybody.

PROF. CAPRON: Right. I totally agree with that. But I thought you said we would know investigators would themselves always take care of this problem because it would be in their interest to make sure that everybody had made advance planning. And I'm just saying, no, if they can

go to the legal representative, they don't care if you have advance planning or not.

And so I agree. I think the statement that we want in the report is that the person's capacity should be reassessed as appropriate and one can never rely on a prior assessment if there is reason to believe it no longer is valid.

DR. MIIKE: Alex, if you look at the flowchart, the left arm has no legal representative. That's the area that I guess we're most concerned with. You look down the left of the chart, the left side.

PROF. CAPRON: Yes. The answer is, yes, the person still is capable, Larry.

DR. MIIKE: No, but fluctuating capacity, that left arm has no legal representative to look out for —

PROF. CAPRON: Because you reassess them and they're still capable.

DR. MIIKE: But what's the mechanism for that?

PROF. CHARO: Right. The problem here is if they lose capacity, that's what everybody is agreeing about.

PROF. CAPRON: I agree. All I'm saying is I don't think it will be self-enforcing. I agree with your final statement, that it ought to be up to the IRB to say to the person, "You've got to reassess this."

DR. CHILDRESS: Okay. Eric, and then Rhetaugh.

DR. CASSELL: Well, I want to hypothesize a specific thing that happens. This study has been going on now for two years, a new kind of instrumentation comes on the scene which is able to trace exact thoughts as they march through the front of the brain. It's irresistible. It's also a little uncomfortable. And permission is going to be asked to do this. It's not part of the original study.

Now somebody comes up, and you think it's to the investigator's advantage to have ensured an advance directive? Impossible. It's to their advantage to cheat and that's precisely what they'll do unless we have some mechanism of having it invoked that doesn't bring their study to a halt. If they have to start the whole complex mechanics again, it will really make a lot of problems. On the other hand, we have to protect those subjects. So we ought to have some mechanism by which either the IRB is brought back into it or some way monitoring is brought back on.

DR. CHILDRESS: I guess following Steve's rule yesterday, if there's this much discussion, it's clear that we need to do something in the report to indicate how this is going to be handled.

DR. DUMAS: Well, we need to be clear about what it is we're debating. What I'm hearing is that if a person is deemed to be capable of giving consent and does so and they are involved in a project, then it is assumed that they would continue in that project unless there is some reason to stop to reconsider the issue. Now, are we asking for reasons to stop in the course of a project to

reconsider consent?

PROF. CAPRON: If there has been a change in the person's behavior or status in a way which —

DR. DUMAS: Okay. Which raises some question. So that is the issue that I think we're debating. The other thing that I'm hearing is that if the study changes, that is another indication to stop and get consent for the study change. But it's the former one that I think people are groping with.

PROF. CAPRON: For the latter, you may need a new IRB to review it.

DR. DUMAS: Yes. And I think we ought to make that clear, the difference between stopping to get IRB approval and stopping to really assess whether this patient is capable of continuing.

DR. CHILDRESS: Right. I think it's your second one that the discussion has most strongly emphasized and where there are issues perhaps still to be resolved.

DR. CASSELL: Remember, that's what makes this the special population that it is. This kind of problem is what makes them the special population.

DR. CHILDRESS: Have we indicated enough for staff to continue to work on the text in this regard?

Diane?

DR. SCOTT-JONES: I have one comment. I would be helpful in these discussions if we referred to specific sections of the text as it is, because we should be debating that at this point instead of something more general than what we've already written. So it would help enormously if we could refer to what we've already stated so that it can be clear how we're saying something different from what is already in the text.

DR. CHILDRESS: Right. Except this particular one is one that staff in consultation with Commissioners felt was not perhaps dealt within the text in a way. So that's the reason for the discussion moving beyond it.

Eric?

DR. MESLIN: Maybe I could just make one what I would hope would be a final comment on this. If the issue is, should the capacity assessment discussion, which we've already agreed is important, and begins on 72 and continues in other places, should it include mention along the lines that Alta. was proposing, that as part of the design and the recruitment strategy, consideration should be given to whether or not that capacity assessment activity should not only occur at the beginning of the study, but should be kicked in or should be alerted later on in the study under particular conditions.

If the answer is yes, something like that should occur, then it's easy to insert language

as early as page 72. What we would need to hear is whether you think that that language should say yes, it should be kicked in in exactly the same way, or simply that investigators should be particularly aware of the possibility and build it in, or some other such combination at work.

DR. CHILDRESS: All right. I'll take a couple more comments and then we need to move on so that we can get onto the other topics.

David?

DR. COX: I'm arguing here for simplicity. I think making a comment about this being a possibility to look at but not trying to micro manage it in terms of detailed regulations and flows, is the way to go. I think that this is only one of many such things that one might be able to think of. And here when we get public comment, if we don't have a million of those, I'll be amazed. So that to have a class of things that we see as potential complications that we want to alert people that we see but that we can't lay out the detailed rule for all of them. And I see this as one such thing.

DR. CHILDRESS: All right. Have we had enough discussion? Are people satisfied with the direction of the discussion? Could we take five or four minutes to finish up, we hope, the remainder. I hope so. So with that time constraint looming over us, the evaluation question that emerges as a possible additional recommendation. Should we include among our recommendations that an appropriate oversight body will evaluate and report on the effects of these new requirements in three to five years? This is something, again, that is not in the text. Is this the direction the Commission would like to proceed?

DR. COX: Harold raised or queried yesterday whether we might consider auditing or other such things. I thought about that last night in my dreams and woke up —

DR. SHAPIRO: Sorry to give you nightmares.

DR. COX: No, actually, it was a good dream, Harold. I'm very much in favor of this. In a number of the public testimonies that we've had and testimonies from different experts, we raised questions about how often does this or that happen, and we don't have a clue. And I would prefer not to be in that situation five years from now and I don't think it requires tremendous bookkeeping to audit how many times a particular protocol gets rejected. So I'm very much in favor of not setting up a commission to just evaluate it, but to be able to have some ongoing collection of data that they'll be able to look at.

PROF. CAPRON: This is very consistent with our other larger project about how this whole process will take place, not with these subjects.

DR. COX: I think it's one of the most useful things this Commission could do to have a way of ongoing collection of data that will be accurate to be able to know what the facts are. Because I think in this field, for myself, that's one of the things we struggle with the most. We have lots of paper and we have no idea how well it's working.

DR. SHAPIRO: Jim, could I make a comment on this? As I think about this, I think

the issue of encouraging the collection of more information—so many of the questions we ask don't seem to have any answers—is actually more important in my view than whether we evaluate what we recommend. Because what we recommend, if implemented at all, will be very slowly implemented over a longer period of time. I don't know where we're going to be in three to five years and I'm not sure that that's, in my view, a high priority. In any case, the world will evaluate it out there whether we say so or not. But the issue of finding some way to articulate the need for more information on how the system is operating, and as Alex said, this relates to a report we should have out next year sometime, is I think quite important.

DR. CHILDRESS: Further discussion on the evaluation, the collection of information? Is there general agreement with the direction Harold is suggesting? All right. We mentioned it in passing already this morning, I think Larry raised it, but we do have Laurie's second point, page 3 of her memorandum, worrying about our recommendation that IRBs not approve research involving subjects with mental disorders that may affect decisionmaking capacity when that can be done with other subjects. She worries about this having an unintended effect of excluding individuals from experimental treatments which can be life-saving.

How do you respond to this concern? I know from talking to several of you that you think this is not as much of an issue as she indicated.

DR. DUMAS: Well, my feeling is that if it can be done with another population, I don't know that would deny people the outcomes of that research that might be lifesaving. So that rationale doesn't quite compute.

DR. CHILDRESS: Steve?

MR. HOLTZMAN: I was just thinking about this. In her example, the trial was an efficacy trial with —

DR. SHAPIRO: I'm sorry, Steve, I can't hear you.

MR. HOLTZMAN: I was just thinking about Laurie's question, and I think it goes like this. In her example, the trial was an efficacy trial with potential therapeutic benefit. Hence, by definition, the subjects must be people with the disease; e.g., schizophrenics. It can't be done in a normal population. That's good as far as it goes. But Laurie's question is, among, for example, schizophrenics, there is a population capable of giving consent and a population not so capable of giving consent, and can we be read as suggesting in that case that it has to be done with those who are incapable of giving consent. That's why she says a potential inadvertent consequence.

DR. CHILDRESS: Thank you.

DR. DUMAS: That helps. Thank you.

DR. MORENO: I'm not sure if I'm understanding what Laurie's concern is. My recollection is that we dealt with this issue under the rubric of the compassionate exception. I don't know why we're sort of reconsidering this question. There's no issue of discrimination for people who have schizophrenia, say, and also have cancer, if there's a potentially lifesaving or life-extending

research procedure for which they might otherwise qualify, then they could qualify under compassionate grounds without being on the study.

MR. HOLTZMAN: I think that's a different issue.

DR. MORENO: Is that a different issue?

PROF. CAPRON: I think she answered it that where we are dealing with so-called potential benefit we don't have an exclusion of these individuals if their legal representative agrees that they should be enrolled as a subject and they don't dissent from that. So her premise, her starting premise is that the report could be read to exclude people from eligibility I believe is an inaccurate representation of what we said.

DR. DUMAS: No, not on this chart. In theory, can this research be done in principle with another population? And if the answer is yes, that does in fact eliminate that population.

PROF. CHARO: Yes, Rhetaugh, that's true. So if you were looking at chemotherapy and you didn't need to use people who had a form of dementia, you would avoid using them. But if the chemotherapy was potentially lifesaving and no standard treatment existed, compassionate use protocols would allow a person who has a form of dementia to have access to that experimental drug off of that study. That's the compassionate use route by which for somebody for whom it genuinely is a therapeutic intervention, it is available on special application.

PROF. CAPRON: But you don't enroll them in the study.

PROF. CHARO: Right. You do your chem. trials with competent cancer patients, and if there is a study drug that is the only available therapy for people who are failing on all standard therapies, it can be made available on a compassionate use basis regardless of their mental status. So if it's a lifesaving issue for me, it doesn't matter whether I've got dementia.

PROF. CAPRON: Laurie's concern is something that isn't lifesaving but it is potentially therapeutic. I think the annals of medicine are strewn with examples of things that were believed that they would be beneficial and turned out to be either not beneficial or harmful, which is why you would usually want people to consent to be the study population.

DR. CHILDRESS: Steve, do you want to pick up?

MR. HOLTZMAN: I'll repeat it once more. If you read what she says, it's specifically not dealing with the cancer trial on schizophrenics. It's asking with respect to what we mean by a population if you have a treatment regimen, a trial for that disease, schizophrenia, can we be read as saying that among schizophrenics, if you've got those capable of consenting and those who are not, are those two distinct populations, and this is being read potentially as saying you have to go with those who are capable of consenting. She says some of these individuals, e.g., schizophrenics, may lack decisionmaking capacity at the time they enter these protocols if exclusion from these protocols could be detrimental to their best interest. The exclusionary clause is what "population" means —

DR. MIIKE: But the answer is in this protocol. But because that distinction is made further down the scheme.

MR. HOLTZMAN: Okay. So that's clear. Everyone's clear?

PROF. CAPRON: Where, Jonathan, is the language which corresponds, as Larry was just suggesting, to that box at the top of this chart as to the meaning of population? Is it schizophrenics versus non-schizophrenics, or capable schizophrenics versus incapacitated?

DR. MORENO: Well, that was made in the approval. In general, the population I gather is the population of persons with mental disorders.

PROF. CAPRON: That's how I was reading it. But where is the language here that would answer this question?

DR. DUMAS: The reason is that if this is a research project that is not specifically focused on mental disorders, then if the person has a mental disorder that can be done with somebody else, then they should not be included. That's the way I'm reading it.

PROF. CAPRON: That's why we should document this therapeutic section and capacity uses section. Do we know where the language is, Jonathan? I'm still looking for an answer.

DR. MORENO: The language is that which introduces the whole report. That is to say that's the population that this report is about is about persons with mental disorders.

PROF. CAPRON: No. This report is about a compound population. People with mental disorders impairing their ability to consent, right?

DR. MORENO: That's right. This is the problem with having a chart, as you know.

PROF. CAPRON: Right. With the chart lost in the report.

DR. MORENO: Rather than attending text.

DR. CHILDRESS: Are you raising that as question? Are you raising that as a research question for Jonathan?

PROF. CAPRON: Yes.

DR. CHILDRESS: All right. Page 170 on limiting subjects.

PROF. CAPRON: That sounds to me as though Laurie is absolutely right. This seems to suggest a policy choice saying that among schizophrenics, our example —

PROF. CAPRON: 170, lines 7 through 10. It says "An IRB," line 9, "An IRB should not approve research involving subjects with mental disorders that may affect decisionmaking capacity when such research can be done with other subjects." Now, our whole process here is to talk about individual subjects being assessed. So it isn't enough that you're in the category of a disorder which affects some people one way or the other, you could still end up on this chart. It's at least ambiguous. And it needs to be expanded to make clear whether we are saying schizophrenics

or mental disorders.

DR. SHAPIRO: Jim, you have three or four minutes to finish this.

DR. CHILDRESS: All right, folks, three or four minutes and three or four speakers. Jonathan, David, and Alta.

DR. MORENO: The point is taken and I understand the ambiguity. We can take care of it.

DR. CHILDRESS: Okay. Jonathan says we'll work on the ambiguity.

David?

DR. COX: What I'm going to do, and I really encourage the staff to do this, it's matching the text to the flow chart. The flow chart is what I used to figure out what the hell's going on here because it's hard reading the text to put this in context. Laurie's pointed out one thing I think on page 170 where it's confusing. And I'm going to spend time doing that. But I think that the staff really needs to spend time doing that because otherwise people will focus on these inconsistencies to obfuscate actually all the good work.

PROF. CHARO: Unfortunately, again I find myself in opposition to Laurie's point of view but I'd like to argue for it. There are two aspects to this population that concern us. One is their historic positioning and the stigmatization, marginalization, et cetera. The second is, in fact, the incapacity to consent. Now I must confess I've always been reading this document to mean that even within disease groups, we have a preference for subjects who can consent, that we recruit among those who can consent before we recruit among those who can't unless we absolutely need to use those who can't. And I have always assumed that's what this means.

I would urge us to take that position explicitly. That it is better to use subjects who can consent for themselves than it is to use subjects who have to have somebody else consenting for them. I think Laurie, in fact, would oppose this strongly. That's the point of her paragraph, you're quite right, Steve. And I think we've at least identified the nub of the debate here.

DR. CHILDRESS: Okay. We have three more comments and then we'll have to see where we are at that point and stop. We have our marching orders.

I have Eric, I have Carol, and then Rhetaugh.

DR. CASSELL: Well, just briefly, Alta, I disagree with you because that is not just a difference between ability to consent and ability not to consent, it's a difference in the population. They are not the same population, except one can consent and one can't consent. The fact of consent is a statement about that illness, and we're talking at this moment in time anyway. So I would cast an opposite vote.

PROF. CHARO: But if you needed to work with people who can't consent because you needed to look at the illness in that form, that's fine. I'm saying if you could look at the illness

in either form equally validly, scientifically, you would prefer to use the ones who can consent.

DR. GREIDER: I just want to point out one thing about this debate, and that again I think we should keep in mind the idea of therapeutic misconception. We're talking here about research and mixing that with lifesaving drugs and the idea about having lifesaving drugs. We should always keep in mind that research is research and therapy is therapy.

DR. SHAPIRO: Jim, just to — I find myself, I agree with Alta on this. That's the position I have. Undoubtedly, there is some cost to any position you take here, you pay something to somebody. But I really think on balance, the dangers are much greater the other way. So when we come down to this, if we vote on this, that's the side I would be on.

DR. CHILDRESS: This will be the last point.

DR. DUMAS: That's where I would come down, too. I agree with Alta. But I think there's another question, and that is the issue of use of people who are mentally ill in studies that can be done on other populations. I don't know whether we have addressed that, I don't know whether we need to, but that is something that gets confused when you talk about who should be included and who should be excluded.

DR. SHAPIRO: All right. Jim, we're going to have to draw this part of our discussion to a close. I want to doubly apologize to our guests. We've delayed over an hour now, and I apologize. Thank you very much for being here. We'll turn to the next subject in a moment.

PROF. CAPRON: There's another topic here, two more topics we haven't addressed at all on this report. One is very small, page 112 and 113, and there's a confusion here between a data monitor and subject monitor, a fundamental mixing of the two. And I would urge that we separate those unless someone disagrees.

The second is, are we prepared to send —

DR. SHAPIRO: I'm coming to that issue right now.

PROF. CAPRON: — out before we have results of our research.

DR. CHILDRESS: That's the next question.

DR. SHAPIRO: That's precisely the issue I wanted to turn to now. And thank you for the other comment as well.

My proposal is that we'll have to produce, will produce within the next couple of weeks, a new draft responding to the various suggestions raised today and the Commissioners have made and I think we'll try to improve it as much as we can. I don't know in that period whether we'll get to the executive summary that was called for yesterday; we may or may not get that done in that time interval.

My proposal is that we generate a new draft which we'll send to the Commissioners roughly two weeks from now with a relatively short turnaround time for comments before we then

put the report out as a Commission Draft for public comment. Now we haven't resolved all the issues, we'll be flagging some of the issues which are unresolved and for which we want some feedback. But I think it is time to get some public feedback on this. It will only be a draft report, it's not our final report.

Yes?

DR. CASSELL: Time, you mean time now before we've incorporated what we've discussed?

DR. SHAPIRO: No, after we've incorporated today's discussions.

DR. CASSELL: Yes, because it may be only a draft but it's the draft we'll get hung with if it has got too much in it that's a problem.

DR. SHAPIRO: We will have another opportunity to see a draft and respond to it. But on a short deadline. We're going to have a short time line when we get to that. But what I want to tell the Commissioners is roughly two weeks from now we'll have a new draft, which incorporates the discussion of the last day or so and have a relatively short feedback time. And if there's something in it that really offends you, that's the time to start jumping up and down and get our attention and we could make another decision at that time.

But the intent would be that we go for public comment on this draft. I think it is time for a larger number of people to see this, see where we're going, and get feedback, and we shouldn't feel at all uncomfortable if we change our minds because of the feedback we get. That's the whole point of it. And we're a finite group and there are other people out there who know a lot about this that might have some insights which are of great benefit to us.

So that's the time line on which we will go. So for those of you that are carefully managing your schedule, Eric, it's now, of course we have a Memorial Day weekend coming up, but roughly the end of the first week in June is when you could expect this draft. We'll keep you informed by E-mail if that schedule changes any significant way.

DR. MESLIN: Just as a request, I know that commissioners have read through the draft. If you have comments of an organizational nature, obviously editorial nature, please send us your drafts with a fax copy or a photocopy rather for yourself. And if you have them with you, leave them with us now, get them to us as quickly as possible so that we can start to work on this immediately.

MR. HOLTZMAN: Is it possible to request that the next draft is redlined? Marked to show changes?

DR. MESLIN: Yes, you can request that.

PROF. CAPRON: And with a summary memo of what you've taken away from here and where the changes have been made in light of that.

DR. MESLIN: Sure.

DR. CHILDRESS: At some point, and maybe do this later, Alta raised a question yesterday about whether we might prepare some sort of document for education and edification for IRBs. Perhaps we could come back to that at some point, not necessarily today, but as you're developing this other draft because that may be a document that could be useful on its own.

DR. SHAPIRO: Thank you. The one thing I wanted to make sure to mention, I talked with Eric and Jim about it this morning, as the next draft comes out, we'll be quite clear on how we feel about regulations versus guidance and so on and so forth and what we'll try for. My own view of that matter is that where we do want to recommend changes in the regulations, we certainly ought to do so. But we ought to do so in a framework, in my judgment, which asks the IRBs to act now even on a voluntary basis pending any changes in regulations that might or might not take place.

With that, let's move on. Apologize to everyone for the fact that we have been running almost late since we started somehow yesterday. And I apologize for that.

But let me now turn to Tom, because we're going to be discussing the material on the human biological materials report. Let me turn to Tom and we'll get in a very few minutes to our guests.

DR. MURRAY: Thank you, Harold. First, I need to respond to a question that many of our visitors have been asking. They want to know if the weather in Cleveland is like this year-round. And as local residents will attest, of course it is, flowers are always blooming and the sun is always shining.

With that as sort of the benchmark for truthfulness for the rest of the day...

DR. SHAPIRO: That's why we have research monitors.

### **IRB Policy Regarding Genetic Research: C. Christopher Hook, M.D., Mayo Clinic**

DR. MURRAY: Why don't we go right to Dr. Christopher Hook and get his statement about IRB policy regarding genetic research? As I understand, Dr. Hook, you are the chair of the IRB?

DR. HOOK: I was vice chair of the IRB at the time the policy was formed.

DR. MURRAY: Okay. Thanks very much. And it's a very highly regarded IRB with ample experience thinking about these questions that Dr. Hook is going to share with us.

Just to give you a sense of what's likely to happen, my guess is, if it's okay with Harold, we'll have Dr. Hook's presentation, some questions and answers, take our break, come back, get into the report. We're going to conduct a discussion in much the way that, or at least structure it much the way that the discussion about the prior report was structured, that is, according to the

memo that was distributed ahead of time, although I have some additional points I want to add to the conversation. The memo is a bit different from the memo for the competency report. And we'll get as far as we can. My hope is that by 3:00 today we'll have come far enough to do the same thing that we're going to be doing with the competency report; that is, do a second draft, submit it to commissioners for feedback, and if we feel good enough about it, to post it as a draft on the web. But we will have to see where we are at 3:00.

Dr. Hook?

DR. SHAPIRO: Tom, would you permit me just two amendments. One, we're going to try to finish today's meeting at 2:30, even though it means squeezing the lunch hour in some way. There are quite a few, including myself, who have to leave at 2:30.

And second, I just want to indicate for everyone else's benefit here that Dr. Hook is also Director of Ethics Education at the Mayo Graduate School.

DR. MURRAY: Thank you.

DR. HOOK: I'd like to thank the Commission for the kind invitation to be with you this morning. I've been asked to share with you our experience over the last few years of trying to craft a policy to assist our IRB in dealing specifically with questions that arise in research involving genetic information and genetic testing.

As not unknown to all the members of this Commission, there are a variety of concerns and risks that arise in genetic testing that we were confronted with quite sharply a few years ago by our investigators, including the risk of stigmatization, potential for insurance and employment discrimination, concerns about breeches of confidentiality, potential for discovering undesired or uncertain information in regards to paternity, risk for disease development, and so on. There was also significant concern about the potential impact in the lives of patients who receive genetic information, psychological and emotional harms particularly, and we also recognized that there was a need to protect a right not to know.

And yet, at the time, there was scarce little guidance provided to us in how to address these different concerns. And as our poor gentleman here, we were trying to cry out for some wisdom in how to proceed. Consequently, the chair of IRB asked me to convene a task force to draft a policy. We took the next six months in order to do this task. Then, seeking input from members of our department of medical genetics, individual investigators who performed a lot of trials and laboratory studies concerning genetic information, received input from these individuals, and then revised our draft. This revised form was submitted to the full IRB, and with some additional concerns our policy was approved in March 1996. Soon thereafter, our DNA Results Committee, or DNAR, was formed, and I will explain what the purpose of that is momentarily.

The fundamental principle guiding the activity of our IRB and, in general, our approach to patient care is the thought expressed by Dr. Will Mayo back in 1910—that the best interest of the patient is the only interest to be considered. And in addition to protecting the best interests of our patients, the goal as we tried to put together our policy was to readdress our

understanding of minimal risk and see if it was appropriate in the context of genetic studies. We wanted to provide some safeguards against premature, potentially over-optimistic enthusiasm of investigators. We wanted to ensure that proper and sufficient counseling and informed consent take place. We wanted to protect the right not to know. We also wanted to provide guidance and education for our investigators who needed to be able to address the wide variety of specimens that would be available for this type of research. And, of course, we wanted to see if we could in performing all of these other areas of concern minimize the intrusion into the work of investigators.

Addressing this question of minimal risk, one of the concerns that we received as we began to submit our first draft of the policy was some protest from investigators saying well, now, genetic testing, genetic research really involves keeping or reviewing medical records, taking blood sampling and so on, all of which would fall under the category of minimal risk by strict physical harm definitions. And yet we believed it was important to broaden the concept to encompass psychological, emotional, or social harm, using as a clinical example our approach to HIV serology and requiring informed consent and so on prior to performing that testing.

Therefore, we made a statement in part of our policy that we thought that genetic research, particularly if there is going to be communication with the patient of the results of that research or inclusion of any of that information in the medical record, will involve more than minimal risk to the participants in almost every circumstance. Now, if there will be no identifiers at all maintained with the samples drawn or with the information abstracted from the medical record so that there can be no link to the source, then we believe that the research could proceed without obtaining prior written consent. However, if there was going to be any form of identifier maintained even in coded form, in that context, it would be the opportunity to break the code and recontact, that we would require full informed consent.

If a previous consent for how that specimen was obtained did not allow for the participation or investigation of other things other than that specifically outlined in that consent, then recontact and consent was required. If the specimen had been obtained with some knowledge that additional studies may be performed of a genetic nature but that confidentiality would be maintained or contact not recur, then a waiver could possibly be obtained in accordance with standard regulations.

We wanted to specify the information that we would require for review for our genetic research protocols: What is the information to be generated? What are the risks of incidental finding, such as nonpaternity? How will participants be protected from disclosure to other family members, particularly important in linkage analysis? Will results be recorded in the medical record? Are there circumstances which would require disclosure to the participant or the participant's physician if not previously intended? Will any of the participants be minors, incompetents, or members of vulnerable groups? Where and how will the information generated be stored, the presence of identifiers, as we've just talked about? What is the risk of inadvertent disclosure? And what are the implications for family members, how will these be addressed as well? These things we require all investigators to have thought about and have an articulated plan or understanding of those concerns.

If information generated in the conduct of genetic research is to be disclosed back to the patient, we required a couple of things be present first. That there be a determination that the results indeed are of sufficient significance to justify disclosure. And that the participant have the opportunity to hear the pros and cons of learning that information and provide informed consent to receive that disclosure.

One of the controversial aspects of our policy has been that if disclosure does occur, that the information be recorded in the patient's medical record. This issue has been readdressed several times within our institution. But our rationale is based on the following concerns. First of all, the alternative to that would be after disclosure the information be included in some sort of a sham history or shadow file. By law in the State of Minnesota and Florida, where we have our centers, any information recorded about the patient that can influence their clinical care, regardless if it's in a separate history or not, is formally part of the medical record and, therefore, is fully discoverable upon request. Therefore, keeping it in some other alternative research file simply does not provide any protection. But if we were to suggest that we were doing that to patients, it might make them mistakenly believe that indeed their information was still fully protected and confidential, which we did not want to mislead them.

We also felt that in many cases the risks involved would be deducible from the family history or potentially altered behavior of clinical course based upon that information. And any astute observer would be able to already assess different risks and be discriminating against the patient on that basis.

Given that case, we were concerned that there might be situations in which a family history would suggest a risk leading to discrimination against the patient, but if the results of the study were negative and we were not allowing that in the medical record, then the patient would be inappropriately discriminated against or receive bias against them. We also felt in keeping with the goals of the medical record, if this information was going to influence patient care, it should be there for all care providers to be able to understand the course undertaken.

We also wanted to reduce the risk of misinterpretation. Much in genetic testing now still is very cautious in its interpretation—what does this result actually mean, what is the actual penetrance and so on of the trait. And therefore a careful delineation of the caveats needed in interpreting the result can be put in the medical record and decrease the risk of misinterpretation. Also, we just wanted to oppose a general trend so often now of fragmenting the care of patients versus looking at them as whole individuals.

To assist in this process of determining the appropriateness of disclosure of information, we believed that we needed a separate group that would serve as an ancillary body to our IRB—analogue to the radiation safety group, pediatric research and so on—that would be charged with looking specifically at protocols involving genetic research. This would be a multidisciplinary group that would try to provide impartial review of the request of justification for disclosure and also to review the method of disclosure plan to make sure that the consent was appropriate, thorough, and clear, and that proper mechanisms for counseling took place.

Membership of our DNAR would include a representative of the IRB; someone from the clinical practice committee, simply because so much of what's going in genetic research is quickly translated into clinical care; a representative from medical genetics; and emphasis that an ad hoc member familiar with the relevant area of medicine who is not an investigator. You will notice that a question that may immediately arise in looking at this list is we do not have a lay member on this particular group. We are rethinking about this. Our reason initially was that because we were only advisory to the IRB and not a separate, independent IRB that once our review was forwarded that the full IRB with the lay members would have an opportunity to review it and then we would get that input at that time. What we're finding though is that even among our deliberations, we think it would be helpful to have a lay member there just to ask questions of and to get some perspective on. So this may be a change that will be coming soon.

What have we learned in this process? One of the first things that became immediately obvious was that the education of investigators was crucial and having an articulated policy was an excellent instrument in doing that. Because during the formative stage there were a lot of different concerns that investigators raised. But once the policy was approved, we received positive feedback from the investigators saying we know what's required of us, we can approach this with those concerns already in mind. And compliance has been good with minimal disagreement. Again, that underscores the value of the clearly defined policy.

We also have found that at least in our institution having this separate group, having the DNAR as an independent body has been valuable. Now this may not work in other institutions. But if you have a very busy IRB, such as ours, where the full IRB meets every other week and they're going to be reviewing 2,000 protocols this year, that leaves five to ten minutes for those that actually make it to a full committee. And yet, as we have experienced, the concerns and all the issues raised by genetic protocols completely derail a meeting and take an hour or so in order to thoroughly discuss and evaluate. Having DNAR as the body to engage and take that responsibility has been very helpful. It has enabled us to also have the time to respond creatively to the unforeseen challenges.

And that's the next major lesson, there are always new surprises, there are always new twists and new complications that no policy can necessarily foresee. Let me try to give you an example of one we just encountered about two weeks ago in which the investigators were looking at a delayed onset illness of relatively catastrophic impact on the patients. Three kindreds were studied. One kindred involved some local individuals, but all the members of that kindred indicated that they did not want to receive any of the results back or ever be recontacted again in the context of this study. The results of the study are quite clinically significant and are to be published. And yet, members of the kindred are individuals who will be in contact with the pertinent medical literature. And so how are we going to deal with that situation of trying to preserve their desire not to know, to preserve their confidentiality, and so on. These are the kinds of issues that a full IRB would be completely derailed if they had to deal with that in full session.

We continue to encounter the concerns about disclosure and including that information in the medical record. Clearly, this impacts the choice a number of patients make in terms of whether

they want to participate in research or not once they learn that information will be discoverable if they learn the results. And yet we, as we reason through it, see no other option but to include that information accurately in the medical record because it will be discoverable in some capacity once shared with the patient.

So we as a group have concluded in the face of these difficulties that there is going to be some need for national rules or legislation dealing with the question of genetic discrimination if we're going to provide access to all the patients that can potentially benefit from this type of research as well as clinical testing.

At this point, I'll pause and see if you have any questions.

PROF. CHARO: Dr. Hook, first, thank you very much. And on a very personal note, I'm relieved because Wisconsin also moved toward having a genetic subcommittee and it's good to know that we're going down the same path you've already tread.

Your approach and the additional details that you provided in the handout strike me as a fairly conservative implementation of the Federal regulations. For example, your committee's decision to presume that little of this research could realistically be characterized as minimal risk due to psychosocial risk strikes me as a conservative interpretation of the Federal regs. Now, we've been hearing from certain parts of the research committee expressions of fear that this is going to be a tremendous obstacle to efficient work in areas that require that you be able to continue to match medical records with tissue samples over the course of time.

I wonder since your implementation, and you didn't mention exactly when it is that you put this into place, since your implementation, what's your sense within the investigator community at Mayo about their happiness with this level of constraint on their work as well as with their ability to collaborate outside since your policy significantly restricts their collaborations to those institutions that follow substantially similar policies.

DR. HOOK: We've been at it for two years. And I can say that after the initial protests expressing concerns you just raised, once we went through the process of explaining to them the necessity of why we had to broaden our understanding of minimal risk, I think most of them understood. They had to have a little paradigm shift in their thinking.

It has been more cumbersome for them, there's no question about that. But yet they are complying. And that's the report that I can give you is that they are trying to anticipate those needs—anticipate the need for the counseling, anticipate the need for the consent—and they're doing it so far.

In terms of external collaboration, that has impacted particularly on one study. And we basically had to tell the investigator that these were the rules that we would live by the patients at our institution and we would ask them to pass that onto the other institutions participating, but that the other collaborating institutions had to understand that perhaps they may not have as many patients enrolled overall because of these restrictions. But there hasn't been any massive revolution yet to have me beheaded or have the policy changed.

PROF. CHARO: Investigators aren't threatening to leave to go to a different institution?

DR. HOOK: No. No, we've not had that happen.

DR. SHAPIRO: Well, you can't recruit, what can you do?

DR. HOOK: In fact, we've had other investigators come in since we've implemented the policy and at first it was very different than what they had encountered elsewhere, but, again, the feedback has been positive. Once they understood the reasons why we were approaching things this way, they said, well, we'll do that.

DR. MURRAY: I have David on the list. Does anyone else wish to be recognized?

DR. COX: I was really also sort of impressed by the idea of having a subcommittee to deal with these issues and was even willing to try and consider taking it further because given the realities of the situation where you have five minutes to do each one. There would have been another alternative, which is that this wasn't a subcommittee of the IRB but it was like a separate thing in and unto itself. And that there are good reasons to keep things together.

But my question to you is just in terms of the nitty-gritty operation of this. As more and more things come into the subcommittee, how effective is the IRB in considering this? Is it really a rubber stamp or should it be, is this going to get so complicated that the structure should be two different IRBs? You see what I'm getting to?

DR. HOOK: And it's a very valid concern. Because when you are that busy the tendency may be that DNAR has looked at it, therefore does anyone have any objections; it's then approved, rather than someone at least presenting the issues again and so on. There is that risk and we've been concerned about that ourselves. Fortunately, thus far the volume has been that after we submit our report, it is reviewed again at executive, and then submitted to the full IRB. So there still is that review taking place. When volumes come up it may squeeze that a bit. I think certainly bringing a lay member over to us is going to be important to make sure that part of the review take place.

DR. COX: And I had one other sort of follow up, if I may, Tom, which is there is an area that you didn't explicitly discuss but certainly is something we've discussed a lot, and I'm sure you're actually dealing with it, which is the issue of the samples themselves. Is this something that's going to be one of the increased complications as more and more volume comes through this?

DR. HOOK: Actually, this has been a specific issue recently taken up by our IRB, not necessarily the DNAR per se, but with the tremendous volume of specimens generated and requests for access to previously stored or banked materials, specimens and so on. We have just completed the work of another task force, setting up a central, organized group to look at those requests, to look at the resource we have, to make sure that other potential requesters for those specimens in the institution have an opportunity to get involved and how these resources are used and so on, so we've actually set up yet another policy to try to deal with the movement and access to the specimens.

DR. COX: And what's the relationship between DNAR and that group then? So, that's another subcommittee of the IRB?

DR. HOOK: Actually, not so much a subcommittee of the IRB, but set up within the Department of Pathology and Clinical Medicine because they are the reservoir of this material. It was to help guide them to respond to requests of the investigators. And, they will basically submit an approval as part of what the IRB will be looking at--a checklist of things that have to be approved.

DR. MURRAY: Okay. Just to let everyone know the status of the list, I had myself next--Harold, Alex, and Steve. If anyone else wishes to speak, just let me know.

Two questions, I'll try to be quick. First of all, thanks very much. That was very interesting, very clear, and commendably brief. On all counts, thanks.

As clear as it was, I have one--I had some questions, just try to puzzle some things through. Did I read between the lines that samples that are acquired in the course of research--for the purpose of research--receive a higher level of scrutiny and protection than samples acquired through clinical care?

DR. HOOK: I hope not. I mean, that was not our intent because, again, the issue is what is going to be done with that specimen regardless of whether it's obtained for research or whether it's obtained for clinical care. What research enables us to do is to prospectively obtain consent more readily than a clinical specimen would. But if we had stored clinical specimens and that was their sole means of acquisition--in other words, patient wasn't asked, "Oh, would you mind if we should also use a bit of this for research?" That same degree of the need for recontact and consent and so on take place if identifiers are going to be maintained. There shouldn't be discrimination between those types of tissues.

DR. MURRAY: There was just some ambiguity, I think, in some of the slides.

PROF. CHARO: Yes, it's clearer in the written policy.

DR. MURRAY: Okay. Good. The second question is: I think your very last point on your last slide was what your group determined was a need for legislation to prohibit medical discrimination. And, I'm just wondering what experience--data you have that says this is an important issue. I mean, are subjects refusing to participate for this?

DR. HOOK: Particularly coming to our familial cancer project. There are a lot of individuals who could benefit from participating in the research protocols, or even in the clinical sphere, as testing has become more clinical rather than research-oriented, who are refusing to do so simply because they know that once they do that, that information could be used.

DR. MURRAY: Thank you very much. Harold....

DR. SHAPIRO: Yes, I was very interested in a statement made in one of the earlier slides regarding the barrier you had for the release of information. You said particularly you want

to decide if information is valid and significant. I believe that's, or phrases--I really would just want you to expand on that a little bit. I think that's a very intriguing idea. I'm wondering how one decides, who decides, what issues come up in trying to decide whether something is significant enough and to whom.

DR. HOOK: Our concern was that as investigators were learning the results of their experiments and so on, that they would make conclusions and want to rush to recontact and rush to inform the patients of that. We thought--try not to be obstructionistic, but at the same time just to encourage people to take a deep breath, to pause, review the situation again, possibly have some nonparticipants subjectively look at that information and say yes, you know, we believe you have something here that is of clinical importance that fits the data...it's hard enough toward going back and sharing that information. And so that was our concern--was to just make sure that sort of impartial--.

DR. SHAPIRO: Well, let me just ask a specific question to see if--help me understand that. Supposing you discover some information which is real about someone, but about which there is nothing anyone can do. Is that significant or not? In the way you think about--?

DR. HOOK: Well, it depends on particularly the action of what the real thing is; in other words, is it something that people are going to be needing to make decisions about? I know in the conduct of their lives and family planning and other things of that nature--these are the things that we would want to be asking and considering. But of course, part of the reason for putting in this step is to say, you know--yes, you found something but if there's nothing anyone can do it's not going to influence their life any way you'd notice, other than potentially take an emotional hit, then we would try to counsel against that or think of some other way that we can approach the issue.

DR. SHAPIRO: Thank you.

DR. MURRAY: Alex is next.

PROF. CAPRON: Two questions, Dr. Hook. One relates to the guidance we can gather from your experience on already stored samples; the other, samples that might be collected in the future. On the already stored samples, the document that was provided to us in advance that has more details than the slide seem to place a very great restriction on sharing samples outside the Mayo Clinic. If there were to be any identifiers--and in fact it says, on page 3, "...The samples are sent to an outside organization or investigator without any identifiers." We had talked in our deliberation for--about this distinction between the repository and what's in the repository by way of identifiers and what in the sample had to be used for a particular research project. Your comment orally just now is that you are that you are exhibiting that issue to another committee, did I understand you correctly?

DR. HOOK : The other committee is facing a technical issue of triaging the requests and helping to distribute a specimen instead of a repository.

PROF. CAPRON: Not the policy.

DR. HOOK: No, sir. Now, let me give you some contacts. The Mayo Clinic has always had a very strict requirement, even before this policy regarding genetic research, in how much information or the presence of identifiers we will release outside of the institution--to outside investigators. We have always tried very hard to protect patients from being recontacted by someone outside the institution that they did not, you know, give consent to, that they don't know who this person is. And so, this is just in keeping with our already existent policy of eliminating or removing identifiers before specimens leave our institution.

PROF. CAPRON: Because having made that broad statement in section--in that same subsection on sharing the data, or sharing the sample--you then go on to talk about consent and suggest that with consent you would allow identifiable data. Is that--?

DR. HOOK: Yes. If it is explicitly discussed with the patients that a specimen will leave our institution, we allow that to take place. Under consent we specify a number of things: If it leaves the institution but there are no identifiers, we let them know that specimen will leave our hands; afterwards we have no control over its use. And if there are identifiers, then we have to be very careful that they understand to what extent and what's safe for us to put in the place to preserve their confidentiality.

PROF. CAPRON: Okay. Now, the question that relates to a future collection of--I was interested in the category of samples--it's on page 2, point 3--of samples with identifiers previously obtained for use in another research protocol, and there you're very firm about informed consent--"If the sample use will go beyond the terms of the original consent, "--and one of the issues that we talked about is precisely what that would mean. Is it enough to say a DNA study or an molecular genetic study or a genetic study or an examination of family history--I mean, in other words, if right now I would collect a sample for use in a study having to do with a gene that has reproductive effects where the concern is prenatal screening, and then five years from now--and I said, and this is being collected for this genetic analysis and we may want to do further genetic analysis and by signing, we'd be allowed to do that. And then a colleague from oncology comes along five years later and says, "I'd like to screen these samples for the patient's subsequent experience with breast cancer and do a genetic screening to see if there's a marker for breast cancer. How do you define in beyond the terms of the original consent?"

DR. HOOK: If in the context of the example you've given, the patient has agreed that some other form of investigation can take place on the specimen other than the explicit one at the time, we would allow that oncologist to have access to the specimen, but we would not allow them to recontact the patient or share any of the results of that until there had been an explicit plan for recontacting counseling to cover the new context, which has just arisen. But if they want to have access to the specimen to do some generic study or whatever, we could allow that.

PROF. CAPRON: But these are specimens with identifiers and so I would assume that if this were an in-house investigator that person has access to the Mayo patient database; and with the identifier, could then see if this patient who was in for reproductive issues five years later developed one of the cancers that I'm looking at.

DR. HOOK: Right. If the initial consent did not specify that any other form of genetic testing may be done in the future, recontact for re consent would be necessary before anything could be done to that specimen.

PROF. CAPRON: I tried to get to how broadly you feel comfortable. It's a matter of genetic research or--.

DR. HOOK: General research. Genetic research. We've tried to be broad in that regard in terms of we want patients to be able to say "Yes, you can look at this but this only" or "I'm willing to let you have access to this for other types of research beyond the scope of your individual trial."

DR. MURRAY: Thanks. Steve . . .

MR. HOLTZMAN: A couple of quick questions just to follow on that last point. If it's collected in the clinical context, do you also go into that kind of specification about what kinds of future research, or do you just go with a "may be used in future research?"

DR. HOOK: If it's a clinical specimen but yet additional material is drawn at that time for research purposes, the patients are offered a consent to allow additional forms of research that is going to be provided.

MR. HOLTZMAN: So, it can be just a very general kind of--any kind of research.

DR. HOOK: Right. What we're trying to do as much as possible, particularly in the genetic ground, if we know that's going to be the questions asked, we'd like that consent to explicitly talk about genetic testing.

MR. HOLTZMAN: So, two more quick questions. The second question is: If you could comment about the second question, how the Minnesota law could be affecting this. The first question is: Imagine I come to you either in Mayo or outside of Mayo and I want 50 prostate cancer samples; I want the complete medical histories. I don't care about the identifiers of the sample and in one instance what I want to do is look at germ line polymorphisms and so I'm looking at vertically transmitted genetic traits. And in the other case, I'm going to look at transcripts from the expression-level differences in certain oncogenes, so I'm not looking at vertically transferred genetic traits but all of the same issues are at stake with the exception of transmission. Would you handle it any differently?

DR. HOOK: If we're able to strip the identifiers--in other words, you have abstracted clinical information and a specimen that have no means of contacting that patient or knowing who they are--no, I would see that there would not necessarily be a reason to discriminate between the two. In regard to your first, which is your second question, you made reference to a Minnesota law which has a bearing upon all research--not just genetic research. The legislature has passed a ruling in the State of Minnesota that no medical record can be accessed for any purposes of a research nature, even for just an epidemiologic study, without there being explicit consent from the patients. So, the old practice of being able to pull up a list of the last 3000 patients that we have seen with this

disorder to try to obtain some epidemiologic understanding about the disease is now going to impact it, in that we have to go through and make sure that all of those histories obtained have given us consent to approach their medical record from a research perspective. Now, 95+ percent of patients have indeed given us their consent and it's now requested as any new patient comes to the institution, but there's still those patients that say "I don't want my record approached for any purposes other than my direct patient care" and this will have a negative impact on epidemiological--.

DR. SHAPIRO: Could I just ask a follow up question to Steve's, namely, he's made the request of a certain amount of material and you've taken the identifiers off of that, and you've sent them onto him providing you have something appropriate. When you say "take identifiers off," does that mean that even you can never trace back where those samples come from?

DR. HOOK: That's correct.

MR. HOLTZMAN: But in the sense--in the sense of which he still has John Jones and John Jones's medical record, and I get No. 1 with the medical record but he gets rid of No. 1 equals John Jones. It hasn't been anonymized in the sense that if you just have a medical record back in Mayo without the individual's name attached. It's just there's no code. The link has been broken.

DR. SHAPIRO: Right. You could not get additional information because nobody knows where that record came from.

DR. HOOK: Correct.

DR. COX: Well, then, an extension on that. I don't mean to cut into the line--.

DR. SHAPIRO: Do you want to use your slot, David?

DR. COX: Yes, this is my slot.

DR. SHAPIRO: Okay, use your slot.

DR. COX: This is my question actually, and I'm sorry to--so now, that researcher has those prostate cancer samples that have been stripped and he says, "My God, you know, I found, like, the cure to cancer. But I just need to know one more thing about those people." Can't he help me? Can you help them?

DR. HOOK: If we truly stripped and do not have a linkage--you know, a list at least--we could help, you know, in that circumstance other than if a generic list--these were the 50--the names of the 50 individuals that we sent out to such-and-such laboratory. If we have not maintained the code, then the alternative would be to say "We found something significant--we think we need to investigate this further in the clinical realm." It would be, I think, justly so to go back to all those 50 individuals and then prospectively say "Okay, your specimen--you permitted your specimen without any identifier--we now have found some information that may be clinically relevant--we are offering all participants an opportunity to learn more about this discovery and whether or not they would like to have more formal clinical testing or involvement occur."

DR. COX: Yes, I've got it. Now, what do you do right now? You said that you strip

things off but that the subtleties of these, this point, are really quite important because if the 50 people, even if things are taken off, are singled--you know, are kept somewhere. Okay, identifiers have been stripped but you still know who those 50 people are, and why I believe this is important is because then they are people that really are a different type, not individually but just as a group. And, so, I'm not putting value judgments one way or another, but just--is this an issue for you right now, or in general people don't ask for that very much or--?

DR. HOOK: Actually, it's important to maintain some record of every trial that a history or patient's material has been included in.

DR. COX: That's right.

DR. HOOK: Because, what we have learned after the advent of the Minnesota statute was there were patients that said "I don't object, but could you tell me of, you know, how many trials has my history been used in and what for and what were the questions being asked?" I think that's very appropriate for them to have access to that information.

DR. COX: But it's a big difference if you have 10,000 who have prostate cancer, and go back and test all 10,000 as opposed to knowing that it was that group of 50, when you don't know exactly who it was but you can go back and identify who they are. And that's really where this issue is coming. And for me it's a complicated one because identifiers may be stripped off, but if you can go back and know who that 50 are, then have they really been stripped off? Right? I just--this is a very complicated, an important point.

DR. HOOK: Anonymized only to a certain extent.

DR. COX: Thank you.

DR. MURRAY: Steve, is that an urgent immediate follow up to this?

MR. HOLTZMAN: It's something I'd ask people to ask about because it's something that troubles me and that is if you look at guidelines like this, if I ask for those 50 prostates and they're good County people who've been there for 30 years and you've got the whole record of them till then stripped of identifiers, you can give me that so I can have the progressive inform--the longitudinal information. On the other hand, if I'm doing the study over the course of a year, and that person has come back in, I can't get that further information. What I struggle with intellectually is why if it's okay if you get the 30-year history up until that point--again, without the identifier--is the problem, is there something problematic about getting the next year's worth of information or is only problematic because in order to get, have access to that additional future longitudinal information, it opens up the prospect of going back.

DR. HOOK: The answer's yes.

MR. HOLTZMAN: Well, we've had arguments from Eric previously that after you start the research if you're going to get new information, they are a research subject and you need consent. So--and I see Alex shaking his head, so I think we need clarification on that issue. Because, again, this goes to this issue of one-way encryption schemes. One-way encryption schemes take care

of--if the nub is the recontact, they take care of it; if the nub is a research center, it doesn't. I think we need to get clear on that.

DR. MURRAY: Well, could you ask them to consent? If you anticipated this, then we will continue to--. Okay, if there's no consent you can't ask. If there is consent, okay. Alta, you've been very patient.

PROF. CHARO: First just to be responsive to Steve. For me, the major issue is the possibility of recontact because that poses the most opportunities for complicated interactions with information that is clinically ambiguous, has the potential to be as destructive as it is helpful with everybody you'd see—patient, doctor, investigator. But I appreciate the kind of generic concerns about invasion of privacy that come up even with the identifier stripped. What I'd like to ask, though, is on a somewhat different subject. It's back to the notion of minimal risk. Now, since minimal risk is a term that is subject to interpretation by each IRB, I'd assume that around the country there are going to be widely divergent views on this. And, in your case, I suspect it's possible that the conservative interpretation of it was influenced by the existence of a State law, since to find things as minimal risk in the context of tissue sample research and thereby potentially get yourself closer to obviating the need for consent for the tissue sample research is still not helping your PIs very much if they need to get consent for the medical record use. You know, it doesn't get you very far if you still need to go back to the patient, so there may not be as much pressure on you to have a different interpretation of minimal risk that allows your PIs to argue for a waiver of consent.

But, in addition to that there's a lot about your evaluation of the psychosocial and legal risks. And I'd love to hear you expand a little bit about how you came to your conclusions on this. It's not that I necessarily don't share the instinct; it's that I've not seen a lot of good empirical data that in fact confirm people's fears about health insurance discrimination or employment discrimination. There's a lot of fear; there are some good anecdotes. I don't know if good empirical information that shows it as a widespread phenomenon and I wonder how it is that you all came to this judgement call about the level of risk this represents in reality to your patients, or are you really basing it on their perceptions in regards to reality?

DR. HOOK: In regards to one point that you made, actually our policy was created before the Minnesota statute came along. So that didn't influence our thinking at all. It was our fundamental concern about recognizing impact that this information can have on individual lives. And you're correct. There are not a lot of good, hard, universally accepted data about this discrimination. There are several scattered reports. One that received a fair amount of press a couple of years ago made the claim that 50 percent of patients who had some form of genetic testing done had experienced some form of employment or insurance discrimination. These were even for things such as being a carrier of a disease—man lost his job--things of that nature. And the problem with that study was that it was anecdote-driven. You know, and how the information was obtained was basically through support groups where patients obviously had concerns and the few that--or hopefully few--that had been actually discriminated against were a large number of people that actually went forward.

Even in the absence of a lot of hard data, though, there was just a concern that could happen, and if it could happen the patient should know about that potential risk. But even more so, particularly myself, I was concerned about the literature of which there is much more that dealt with the emotional impact of learning this information, particularly in some late-onset neural degenerative disorders--the high amount of depression, suicide risk, things of this nature, even within the malignancy literature--the rising data. It talks about the need for psychological or psychiatric counseling, depending upon the result. Twenty-five percent of some women learning about their one positivity needing some additional assistance. It's the 10 percent that test negative that have problems with survival guilt--survivor guilt--and issues of that nature. That was significant enough to us to really drive our concerns about re-looking at the question of minimal risk.

PROF. CHARO: Okay, thank you.

DR. MURRAY: Thanks. Now, I have three names left on the list: Carol, Larry, and Bette. I know that we all have our longer and shorter versions of questions, so I'm going to ask you to use your shorter version or I'll ask Dr. Hook to give his shorter version of answers so we can break as soon as possible. Carol...

DR. GREIDER: Most of what I wanted to bring up has already been brought up in the discussion that we just had about identifiers and stripping identifiers. So, if one says when it's truly stripping identifiers, but yet you know who those 50 people actually are, the conversations that we've had in the past--we wouldn't really consider that necessarily completely stripped.

And to get back to the issue that you were just discussing with Alta, which is the psychosocial impacts--if you know who those 50 people are, and this was supposedly anonymous research and yet you can recontact those 50 people and say "Well, there's a study that's ongoing using your sample and..." you know, "...maybe one of you has something interesting in there. Would you like to participate in a further study?" That would have significant psychosocial implications. So, simply by "stripping identifiers" in your definition does not necessarily protect against these kinds of recontact issues.

DR. HOOK: There are protocols that we write or encourage the consent to be written in such a way that patients allowed the opportunity to say "no contact" will occur for any reason so that they have prospectively stated "I don't want to know period. Even if you find something, I don't want to be recontacted." And I think patients should be given that opportunity, which may help at least those patients that know that this is going to be a potential--.

DR. GREIDER: But if they came in--we've had many discussions about people who come in in the context of clinical care and the mental state that people are in when they have to sign some form they don't necessarily know what they've signed. And then those are supposedly stripped of identifiers and those 50 people are sent on and then they're recontacted, not really being aware that they were in research at all.

DR. HOOK: They should never--you're making an assumption that there's never a discussion or some verbal interchange in addition to giving them a form to fill out, which at our

institution should not be occurring and isn't, hopefully, to my knowledge. That if a clinical--if a research specimen is obtained at the time of a clinical specimen, that consent form, that discussion, should indicate either that there will not be any recontact or any circumstances, or in the event whatever the investigators think may happen so that that individual has some advance warning that recontact may occur.

DR. GREIDER: But I'm not talking about research at all. I'm saying somebody came in for, you know, to have some of their colon removed. And then--and there was no talk about research. And then that sample is stripped of identifiers and sent on, which I think could occur in your protocol. And then they are recontacted saying, you know, of this--you know--these 50 people, you were one of this set--.

DR. HOOK: Right.

DR. GREIDER: And so what is really stripping identifiers in--to protect people that don't necessarily have knowledge of being involved in research?

DR. HOOK: If there is no prior knowledge of any chance that research occurs, I can tell you that our goal would be, as much as possible, to anonymize any recontact. In other words, to simply minimize any potential--you have been a previous patient at the Mayo Clinic with a prostate biopsy. We are contacting everyone who has had a biopsy to potentially participate or learn in a new study. It would have to be done prospectively that way. If there was no knowledge that the patient had--that they are participating in a study, then we would need to minimize the potential for them to be concerned other than the fact of what they know about what they participated in. "I was a patient who had prostate biopsy."

DR. GREIDER: I wasn't criticizing anything or asking for a specific question. I'm just trying to highlight the issue of what is stripping identifiers and, you know--and then you even brought up the question of you can sometimes strip name, Social Security number, address and still have it be identified by the person reading the journal and recognizing their own pedigree or some other--somebody else doing some other DNA tests, so--so it's not a simple issue of stripping identifiers, which is what we have been grappling with most of the time.

DR. HOOK: I agree with you. I mean, this is the creative part of what we're all trying to do right now, to preserve confidentiality when there are so many potential leaks in the system.

DR. MURRAY: Larry....

DR. MIKE: I pass.

DR. MURRAY: That was very brief. Bette....

MS. KRAMER: My question is about the consent procedure. You did not share with us your sample forms. They'd be interesting to take a look at, but could you just tell us briefly how you handle the consent procedure and how you handle it specifically in the clinical setting? And, could you give us a evaluation as to whether or not you think that these people are truly informed?

Because we've been concerned about people who come in the clinical setting who are understandably traumatized by whatever's going to be done and they sign and that's it.

DR. HOOK: I did not share with you any sample forms because we have not generated any sample forms. There are so many specific new ones that no single forms may be able to encompass all the basic instructions of genetic inheritance, and we do have sort of a sample of that.

PROF. CHARO: Eric, if I may--just for your information I'm happy to share with you as well as Bette right after this. They are the Wisconsin model forms. With all the different modules.

DR. HOOK: And I want to look at what you have done, but we have tried to articulate more pieces of information that the investigators should include rather than having a generic form. Part of the process of our review is to ensure that consent is adequate is the inclusion of a genetic counselor, DNAR to review to make sure that the information concerning that specific diagnosis being investigated is sufficient to allow the individual to understand the process that is being studied, the type of information generated and so on. We have in some cases asked formally that there be a medical genetics consultation occur during the initial consenting process so that they can determine if they want to learn the information and participate in this study or not. Others have not necessarily required that. The degree of involvement depends on the disorder in question.

MS. KRAMER: So, if I were to come in to the Mayo Clinic for a stomach biopsy, I would not be asked to sign any form that would permit my tissue to be used for any kind of genetic research on admission, and my clinical sample would not be available for genetic research unless I was recontacted?

DR. HOOK: No. You would not--if there was going to be research done and we knew that that was going to be the case, then you would be contacted prior to your endoscopy and given the opportunity to participate in this or not. If we have biopsies that have been obtained for research purposes, which you would need to sign a consent for anyway because the biopsy — gastric biopsy is not minimal risk, so you would have to have given us permission to obtain those additional specimens in some capacity anyway. But, let's say that it wasn't specified and we wanted now to do some specific genetic studies which may involve recontact of yourself and so on. Then you would be formally recontacted to participate in that way.

DR. MIKE: But you've left unsaid though, for those people who just come in for surgery or whatever, that you never use their tissues?

DR. HOOK: No, we do. There are discarded tissues. The issue is--.

DR. MIKE: Oh, but, but you were just--in response you were just saying we would anticipate research, etc., etc. I'm talking about the case where you're not anticipating research and you have the tissue. What happens then?

DR. HOOK: So, if you have a section of resected colon, which would be removed purely for clinical purposes, if there is no identifier then the research proceeds without need for recontact. If there is explicit maintenance of a contact of that information, the patient identifier, and

so on, and there would be the desire potentially to recontact the patient, then recontact would have to occur.

DR. MURRAY: Alex had a brief follow up.

MS. KRAMER: Well, all right, but in terms of your concerns about psycho-social harm, I've come in now, you've taken my tissue, I won't sign any consent form for DNA research but my tissue is sitting down there in the path lab that, subsequently, you stripped of identifiers, and then I come along and I read an article in the journal about research that was done at the Mayo Clinic on patients with exactly this problem and these are the proven, you know, and this is--subsequently the DNA research and this is what's been shown.

DR. HOOK: And your concern is--I mean, are you concerned that your specimen was used for research purposes?

MS. KRAMER: No.

DR. HOOK: Well, you would have--by our Minnesota statute, you would have signed upon entry that information may be obtained for research purposes that may not necessarily be linked specifically to your name and to your record. So, you have already signed the consent for that. If you had said, "I want none of my medical record, which includes tissue specimens, to be used in any form of research," then your specimen would not have been part of that cohort that was sampled or studied.

MS. KRAMER: And your--and your consent procedure covers these--covers these patients coming in for clinical procedures?

DR. HOOK: Yes, because tissue specimens are by definition part of the medical record.

DR. MURRAY: You want to follow up, Alex?

PROF. CAPRON: I did have one question following up on this. Is it your sense as an informed and experienced IRB person that you were hired to do that, or did you read the Federal regulations to make that simply an option that you had in treating research with stored tissues samples?

DR. HOOK: We--I'm going to answer this--we felt a strong moral obligation to protect our patients' interest as best we could in a number of spheres. The federal regulations implied some of these concerns were not explicit, and that is why we felt the need of generating our own policies, be more explicit, and deal with different types of specimens.

PROF. CAPRON: You did not feel required.

DR. HOOK: No.

DR. SHAPIRO: Thank you. Let me just make one comment--really two comments here. One is on the issue that has been discussed back and forth here about maintaining a list and the

fact that that doesn't ensure in the sense we've talked about that were unidentified because you do suffer some risks because you might be identified as a group that has some risks associated with it. It's also true--I was discussing this last night with Dr. Hook, and there's another aspect of this and that is if you take a little different view and think that you may encounter what you feel is an ethical responsibility to recontact someone and the maintenance of a list has that potential benefit as well as the potential harm that's identified. It would be interesting for us to think through some things like that as we go ahead, but we'll come to that a little later.

Well, I have good news and bad news. The good news is we're going to break for 15 minutes. The bad news is I'm going to recommend that we work through lunch. We'll arrange some kind of logistics to get people a sandwich or something like that. But let's break for 15 minutes. Thank you very much.

DR. SHAPIRO: As I say, we're going to try now to meet from now to last through 2:30, but I would expect to adjourn at 2:30 for those of us who do have to make planes. It doesn't--others may choose to sit around and pursue some of these matters further, and I certainly hope that will happen. Fortunately, I will not be one of them, so you'll be free of those opinions for the latter part of the afternoon.

#### **Discussion the Research Use of Human Biological Materials Staff Draft Report: Thomas H. Murray, Ph.D., Kathi Hanna, Ph.D., and Commissioners**

DR. SHAPIRO: I want to just say a word before I turn this over to Tom about where I see the status of this draft, and I think it's in a somewhat different situation than the one we just considered, and our objective here is to try to get another staff draft with specific recommendations to the Portland meeting. That's where I'd like to end up and that to be hopefully that we feel good enough then to be able to send that draft out for some comment. That's where I think that I see the logistics where we're going. I think that's appropriate for two reasons: One is the number of issues which we've not resolved here yet and have to be faced up to particularly in the recommendations area and so on; second of all, just the amount of work that has to be done would not allow us to carry them both forward in a thoughtful way between now and the Portland meeting, where we'll spending most of the next months I'm quite sure on the--. So, that's where we're headed, but I think I'm now going to turn the discussion over to Tom to lead us through that. And I think I'll leave this to Tom. I think that he wants us to consider some of the points--let's get an initial reaction--some of the points that are listed on page 2 of the memo. Then of course we do have to get on to considering whether we identified the right areas of concern--IRB consent, education, regulations, so on--and see what recommendations that flow out of that.

DR. COX: Harold, can I make just a process comment on what you said, that I think particularly for this--Carol and I were just talking about this--in the context of tissue samples report, even more than the other previous report, is that we've had really lots of discussion about different points but emphasis--that is, the process by which staff selects the emphasis has not been completely

clear. This idea, in my view, of having points to consider that we can go through I think is really very powerful. We have it now in terms of both papers. It doesn't mean that those points are all-inclusive, but certainly when we discuss them they get incorporated and highlighted big time in the reports, so I think that that's very useful. We have a very long list today but it probably still isn't inclusive, so I really just wanted to say I think that that process is really a great one and it's likely to get us a long way.

DR. SHAPIRO: Okay. Tom....

DR. MURRAY: What I'd like to do is make some very brief comments about the character of the report that I hope ultimately is produced from our deliberations and then go to the May 14 memo and work through the points there. I'm going to want to add a couple, but let me start with my comment about the nature of the report.

I seek a virtuous report, but I think--the virtues of reports are such things as elegance by which I, and then part of my early training in mathematics we tend to regard elegance not in the rococo fashion but as simple, brief, and clear. And I'm going to at least urge us to do that every time we can--to offer those characteristics.

For our policy recommendations I hope will be only as complex as is unavoidably necessary to be sensitive to genuinely important ethical considerations and practical considerations. Now, there are many smart people on this Commission. We're all very good at multiplying difficulties, imagining all sorts of complex conundrums--and that's a useful exercise to go through in thinking about what you want put into your report and recommendations. We will at some point, though, need to fish or cut bait and decide what counts as important and needs to be accommodated in our specific recommendation and what issues are relatively insignificant, and when in doubt I'm going to urge us to opt for the simpler approach.

The report itself I hope will be, as it ultimately goes into the hands of its readers, easily understood, straightforward to implement, and yet simple enough to be readily adaptable to new knowledge about genetics, new knowledge about--new ideas about research methodologies and other such factors. So, those are pretty ambitious goals. I would put them on the table.

Now, let's go to the memo. The general points— does anyone wish to raise any questions about those? Some of these are just basically apologies. We still have peer review to go through. There's clearly a lot of copy-editing that needs to be done. If you have any particular suggestions, I hope you will forward them to the staff, as I will. References are not complete and need to be checked. Chapters 2 and 3 were--the order was reversed. There are cases in chapter 2, and if you have other ones you think would be useful to add please do so. Alta...?

PROF. CHARO: Did you ask for general points?

DR. MURRAY: Yes, general points.

PROF. CHARO: I mentioned on e-mail; I'm not sure if I did it to the entire list or only to the staff. I'd like very much for us to address the issue of State medical records laws in the

context of this report because I know I and several others have already anticipated the interaction between that and tissue research. Today we saw an example of it in the discussion from Dr. Hook and I don't think it'll be possible to do this as well as we would like to do it until we integrate this.

DR. MURRAY: I don't recall exactly, Alta, but the first sentence of the chapter on regulations, chapter 5, I guess it is, says "U.S. landscape looks as follows:..." There's Federal regulations; there's this, that, and--. It actually contains no mention of States. And so I'm really very glad that you raised that. The question I have is whether there are other kinds of State regulations or does that phrase in use State regulations regarding medical records really the only one we need in this case?

PROF. CHARO: I'm not sure what phrase to use until we've seen the research done, and that's really a question about whether or not we have on staff somebody who can do it or--when I wrote the section on the regulatory stuff, it was simply to explain how the Federal regulations operated because we hadn't had the force for a while. A simple flow. But very shortly after that it was completed, it seemed apparent that for the purpose of discussing the recommendation, we would be debating the degree to which we wanted to give PIs a relatively free hand or restrain them by the need to go back and continually get more or more detailed forms of consent from people. And that debate would seem pointless if they already were, for most of the kinds of research they wanted to do, going to have to go back and get that kind of consent anyway for medical records use. If they did have to do that, then there was no added burden getting that consent for the tissue use at the same time and the debate would be--really, it could never benefit them. And that--I don't know if it's going to be in State legislation, State common law, both--if some of it will be done in regulation. It could be all of those sources, and it's not a trivial piece of research, especially if you want to try to cover the national landscape. We know California has a medical records privacy law; Minnesota obviously has one. I don't personally know how many other States do have a well-developed law on this subject and how many IRBs are even aware of the fact that they're subject to that State law. They may be blissfully ignorant in many cases.

DR. MURRAY: I'm convinced Alta's right about the need to do that. Can I just follow up on this, Rhetaugh? Does anyone have a--if anyone has a different view let's get it out. But do we agree that some survey of State laws as they pertain to medical records--?

PROF. CHARO: Medical records research.

DR. MURRAY: Medical records research. And it's particularly--of course, also, if it would include explicitly tissues. Obviously, but we're probably not going to find--. We agree that that needs--that research needs to be done and something of that needs to be redacted and put into the--into our report? If that's agreed...do we have the capacity to do this?

DR. MESLIN: Yes.

DR. MURRAY: And I thought--I thought we might have the person who could do this and so I think we should--would you be willing to talk with the staff about just how to structure this?

PROF. CHARO: Sure, I'll be happy to work with her.

DR. MURRAY: There's something in your expression indicates that you're not saying everything you're thinking, but--so, shall we talk later?

PROF. CHARO: I think this is a pretty substantial piece of work and although we probably won't get very far today in our discussion of the recommendations, it's possible that the result of this work could affect the recommendations. It depends on how the debate goes. So, the scope of it may not be clear till the end of the day--why don't we hold it till then?

DR. MURRAY: Yes, that's what I meant--after today, yes.

DR. SHAPIRO: I have--I just have a question on information here. The first time I thought you said you were interested in State laws, regulations, common law or otherwise, regarding medical records. Then I heard medical records research. I just want to know whether you're--what distinction you're making.

PROF. CHARO: Yes, what's going to happen--what's going to happen is that a lot of these--to the extent that these laws exist, a lot of them are going to talk more generally about access to medical records. The paradigm probably in mind is going to be that of clinical use, and there may or may not be language that applies to research or it may be that by reading it one can infer that certain rules ought to apply to research. There may be genuine ambiguities where there's an absence of guidance on this, and that's why it's not a--it's not a trivial piece of legal research necessarily. And having done 50-State surveys in its earlier incarnation, I know that it can look simple when you begin, and then get--it's full of judgment calls.

DR. MURRAY: Thank you. Rhetaugh, thanks for your patience.

DR. DUMAS: I have--I don't know whether this belongs under general points, but there are sections in the report that I think are overarching and I didn't--I'm not clear about whether these are going to be independent reports or whether they're going to be provided somehow together. The one on human subjects and...

PROF. CAPRON: Separate.

DR. DUMAS: ...and the--separate. They'll be separate. Because the whole area on framing the ethical issues is general, and it seems to me to be as relevant to the report of the other subcommittee as it is to this one.

DR. MURRAY: If I may comment briefly on your point, I think the commissioned paper that Alan Buchanan did for us does have a much broader use of human biological materials in research. Aspects of that--I think the paper is excellent. Aspects of it are--not everyone's in agreement, and I'm not sure how much of the paper will also ultimately end up in our final report. I think you've got--that chapter will probably be substantially edited down. But I would--I want to turn to the specifics of that later if we have time.

DR. DUMAS: Okay. Good point.

DR. MURRAY: Carol...?

DR. GREIDER: The fifth point under General Points says we have included a number of cases throughout the text but specifically chapter 2, other cases will be developed as needed. As I read chapter 2 there are a lot of generalities in there--how things are done--and I don't see maybe but one or two specific cases, and I would really like to encourage getting some specific cases and, you know, staff--pinpointing commissioners to grab 'em out of there or we--going back to ones that we've discussed in the past. In our subcommittee meetings we discussed 10 or 12 specific cases and I think David Cox brought some up at a full Commission meeting. And I would really like to encourage having more specific cases although it states there are some.

DR. MURRAY: Do we differ on what's meant by "specific?"

DR. GREIDER: An example. When you say in general this is how linkage equilibrium studies are done, and then give an example of why would it be pertinent to the general public, we can find the gene--for example, this gene was found for colon cancer, and because we found the gene for colon cancer we can now do screening of individuals and it has an impact on their health. So, why would it be relevant to people? It's because it would have an impact on their health that we were able to do this linkage, this equilibrium or whatever study. There were very specific—human impacts aren't in that one.

PROF. HANNA: We have a lot of cases that we can draw on, and I think one of the things that we've been waiting for is to see what recommendations emerge and then we can more carefully select cases that we know will illustrate the points that you're going to try to make to justify the recommendations. So, I think that--that the whole report will be more fine tuned as you get closer to developing recommendations. So, any cases that you think illustrate a specific point--if you could just let us know and we will include them in there and probably reorganize that chapter around the points that are being made rather than around the research.

DR. GREIDER: Okay, that's fine. I just feel like we have brought a number of specific cases as examples through all of our meetings, and it should be on all the, you know, the transcripts, and the fact that it's stated here that a number of specific cases are included. I just wanted to highlight that. I feel like they're *not* included. And so, just that that needs a lot more fleshing out.

DR. MURRAY: Is there general agreement with Carol that it would be useful to have more fleshed-out cases to make the points we think are key points? There's general agreement with that? Eric has his hand up, and I'm not sure if David is just--with his hand up or--?

DR. COX: I agree that when we know when the key points are, then we can flesh them out.

DR. MURRAY: So, that's a goal for the next draft. Does anyone else wish to speak to the general points in the memo? Or to raise other general points about the document?

PROF. CHARO: I just wanted to thank you because it's gotten enormous and far

more complete. And it's just been kind of a miraculous transformation in a few months.

DR. MURRAY: Alex...?

PROF. CAPRON: I'm not sure if you think the best way to focus our limited time is to go through all the points for discussion, or if there's an underlying question which is to what extent do those things where we have some direct or indirect potential influence--namely, the behavior of IRBs, the shape of Federal regulations, or the possible shape of State laws--now not adequately address and deal with the issues that we have seen arising from the use of stored samples that already exist or policies toward future samples. To try to narrow down what we do *now* by looking at--specifically at the recommendations that would be necessary because they would say Federal regulations are not adequate, or IRBs are not now given adequate guidance and just focus right in there. I think the rest of the report will flow once we have that in hand.

DR. MURRAY: Larry and David and Bette.

DR. MIIKE: The letter--I'm talking around the subject, let's just get on with our--with our conclusions and our recommendations and then fill in the gaps around those. Otherwise we're never going to reach closure. I'd like to walk away from this meeting with a good sense about where we're going and where we've gone.

PROF. CAPRON: I agree, and that's why I think we should focus on where policy isn't adequate now and we recommend changes in it.

DR. MIIKE: Well, before we say where policy is adequate now, we've got to reach our conclusions about what we want to say in this report, and that's where I'd like to go.

DR. MURRAY: What I couldn't tell from Alex's comment was whether you meant that--we really have five bulleted points for discussion, page 2 of the memo. My guess is I should never underestimate how long we can talk about anything, but my guess is we can go through most of them pretty quickly. And then--or do you see this as an alternative to going through those points?

PROF. CAPRON: I thought it was a sharper focus, but I--Larry thinks it's not.

DR. COX: So, I for one want to walk out of here knowing what we're talking about, but I'd like to spend five minutes going through these five points. They're definitions, and one of the reasons why we're in difficulty is because that--we didn't have a common language to deal with this. So, I--

DR. SHAPIRO: I think that's right. I think we do have to go through these points. If it takes us only a minute, we'll take the minute; if it takes us longer, then we need to go to more substantive issues.

Is there another--did you want to say something, Larry? Let's go through the points--.

DR. MURRAY: The first bulleted point about terminology, the terminology used by the Commission. It's now in chapter 2 and the way we've broken it out is there are two categories of materials. Now, remember they're materials that have--that have no way of being linked or

identified, and there are materials in the banks--the tissue samples--that can be linked. So they're--so they're fully anonymous or--.

DR. COX: Actually, Tom, the names specifically in the report are "identified" and "unidentified."

DR. MURRAY: Okay, that's--thank you. We should be using the terms we used. Do we agree that that's a meaningful and useful distinction?

DR. DUMAS: Yes.

DR. MURRAY: I think so. I think we've reached that. Just going to reconfirm that. Now, we have four categories of samples.

DR. COX: Those are samples.

DR. MURRAY: Samples. Right. Do we like the names and the descriptions of the four categories? Carol...?

DR. GREIDER: I want to agree with everything that we discussed before that; in general the spirit of what is here I completely agree with. I have a lot of suggested language to simplify these. It seems like to go on for three or four sentences to make a definition is a little bit excessive. And I don't know if we want to get into that here...

DR. MURRAY: We don't want to get into language here.

DR. GREIDER: But I would like to simplify the way these things are stated and maybe reword it a little bit, but I agree with the meaning.

DR. MURRAY: Do we agree that the four categories are the ones we ought to use if we may choose to relabel them?

DR. SHAPIRO: I think I have a issue of substance here, but I--and the issue on my mind is whether it really is important to carry four categories of samples forward, trying to make small distinctions between linked coded, unidentified, fully identified--whether those, when you come to think of the protections that we're going to recommend--whatever they may be--really have any salience or whether we could really carry the whole thing through by thinking of unidentified samples and identified samples and not get in discussions regarding just how the coding is and how difficult it is, easy to break, hard to break--and I don't know how we're going to deal with that in the end, so I'm just asking the question whether the four as opposed to the simplified two--I don't mean simplified as a, by itself, advantageous--is a benefit. But Carol or David or someone could help me with this. Do you--?

MR. HOLTZMAN: I think there are a few different reasons why we might want to carry through at a certain--a different level of detail--at a higher level of detail--partly is because we happen to be engaging the community here who has been using and hearing these different terms. Right? And so, that even if we end up putting together a recommendation that covers more than one category, that will make it clear and useful, my major concern with how we've done this is--thinking

pragmatically of its utility—is that making it clear the difference between a sample and the research material. It's almost like naming conventions. Maybe you call it--instead of biological material, you call it repository material; instead of calling it a sample--research sample. And then you take that through--it'll be clear to the people who want to use this. So, that would be an argument for keeping it articulated and making it very clear.

DR. SHAPIRO: Go ahead, Larry.

DR. MIKE: I agree with Harold. I think--I don't see this report as being just for the research community, etc. It should be readable to the public and I think it should be called identifiable and identify--identifiable and unidentifiable, in the sense that these other areas fall within those, because we're going to run across the nuances around what we mean because those quoted issues that you talked about with 50 samples that are--you can't really get to the individual but there are ways of getting to it. It'll just get--will get lost in the morass of detail so I'd rather start off with a very simple description.

DR. MURRAY: I just see--I see one major problem with that, at least one, and that is that, you know, the distinction that Steve just reinforced, which is--it's a crucial one for us, which is--what's in the repository may be identified. But when it becomes a research sample it may be unidentified because we strip it. What goes to the research room you can't get back. Does everybody agree that's a possible category?

PROF. CAPRON: Actually, that's not the way it's defined, Tom. Unidentified samples are only those supplied from unidentified materials.

DR. MURRAY: But to describe that as identified...as it goes forward would be misleading.

PROF. CHARO: May I ask for a point of order with permission? Because I think we have a chicken and egg issue and we've been spending a lot of time on the egg over and over and over the meetings on these definitions. One suggestion that was made early on is that it's possible we may never know what we really need until we actually work on the recommendations, and having seen the discussion begin to devolve into one that's very familiar I find myself asking as a point of order, if you might reconsider the need to go through these points that were outlined here and maybe jump to the recommendations as Larry and Alex were suggesting, and then work back to what distinctions need to be made analytically and then which ones need to be made for the purpose of appropriate communication to the various audiences. Maybe if we begin talking about the chicken the egg will get easier.

DR. COX: I second that point, and the only friendly amendment I make to it is that we use these terms that we have written down right now, because so far in this discussion that's not what we've been doing, and that if we--I don't care what we call things, but I'd like everybody to be calling them the same. We have some language here. Let's use it and use it as precisely as we can, and then--and if we could just say that--it doesn't mean that we buy into it. That's all the things that are going to go on. But then we're talking one language with these definitions. It doesn't mean

we've--it means that that's what the report's going to be, but at least we can talk to each other and then move on to say with these terms. What is it we're trying to get done?

DR. MURRAY: I like what David just said very much. I think, at least for the purposes of getting through the day, let's use the terms that are in Kathi's draft. Is that okay if we just work with that for now? We may in the end go back and abandon or collapse some of them.

I'm also--we did a little experiment to see if we could get through the points quickly. May we should say the experiment we tried the experiment--okay, it's time to move onto the next strategy and maybe we should begin to talk about recommendations. That--that's what you were saying, Alta?

PROF. CHARO: I guess I would be the third vote in favor of that just because I'm curious. It's been so many months. Well, the point 3 really is getting at recommendations, right?

DR. MURRAY: Point 3 really does get us to recommendations. I'm willing to do that if others are comfortable with that strategy. Let's talk about what we'd recommend and then we can go back and reconstruct the way we get there.

DR. COX: But Tom, this is directly relevant, then to point 3, and it's in keeping with what I just said, because point 3 uses terms that are different from--it puts in a term of anonymous. I don't know what that means, so what I'd like to do is figure out —.

PROF. CHARO: Which point 3 are you talking about?

DR. COX: This is a table. The flowchart.

DR. MURRAY: Is that a useful way of structuring our conversation about recommendations?

PROF. CHARO: Which flowchart are you talking about? Table X?

DR. COX: I was talking about the one at the end--.

DR. MESLIN: Table X.

DR. DUMAS: Bottom of page 198, one that goes--.

PROF. CHARO: And these--okay. These tables simply explain how the Federal regulations operate. They don't get--. Okay.

DR. COX: Okay, fine. Never mind. What I was--I was actually talking about something else, but this is fine.

DR. MURRAY: You talking about these other tables, David, that are at the very end of the chapter?

DR. COX: Correct. But it's also not--if we're not going to focus on them right now, I don't even want to worry about it, so--.

DR. MESLIN: Maybe a clarification of what the documents are that you're referring

to. Table X or 10 is a table that is intended to complement the portion of chapter 5 that describes what the current regulations say. It was a table that had been requested by Commissioners on a number of occasions and thanks to Alta Charo's very helpful writing we were able to incorporate that table for the Commission's benefit. Table Y on the next page is intended to be a table that that informs investigators with respect to informed consent requirements, also using the existing regulations. These tables do not refer to NBAC's recommendations on this subject at all. We made it clear, or tried to make it clear, that we were not going to produce a table documenting recommendations since we have not discussed recommendations. You may choose to use either of those tables, plus table Z, if one were to be created, or z', to say how do the recommendations that we are discussing map onto the existing regulations, diverge from those recommended regulations or not, so...I hope that's clear. And when we said "flowchart" in the memo, we weren't referring to a flowchart of recommendations, so I apologize if that was misunderstood.

DR. DUMAS: So, the suggestion is that we go now to the recommendations, is that--?

DR. MURRAY: That's the suggestion.

DR. MESLIN: At the risk of pushing this forward, one of the ways of talking about recommendations—consent, IRB review, recommendations, education—and encourage Commissioners to come to the meeting with ideas and should not feel compelled by any of the suggested ideas in that memo, which is on the last page of that memo.

DR. MURRAY: No, go ahead, Alta.

PROF. CHARO: And to that point it seems like one possible way to begin would be as follows: We've now come to understand the current structure, putting aside whether or not everybody in the United States does. We finally do, which basically says that for identified samples, whether coded or by name, there is a presumption that you have to get consent from the tissue source before the tissue can be studied. That's the way the current rules work. And there is an escape hatch. You can get the--you can get the consent waived if it's minimal research and it's not practical to get consent, basically. But that's the way it's set up, and a very big initial cut is whether or not we are happy with that or whether we want to tighten it or loosen it. It seems to me that that's a very important first cut because if we change that basic approach it means that we're now going to be proposing something that is at odds with the current regs. If we tighten it, we can do that by exhortation to IRBs. If we loosen it, it means we have to engage in the regulatory machine.

DR. SHAPIRO: The purposes that we're discussing today, what is considered--I'm trying to stick to David's exhortation to use the right language--but what is considered in the current regulations as "identified" would be three of the four categories that are on page 31--30 or 31. So it included directly identified, coded, or linked, to use our terminology.

PROF. CAPRON: Are you saying two or three categories?

PROF. CHARO: Two of four.

MR. HOLTZMAN: Samples and identified samples.

DR. SHAPIRO: Let's make sure that I know--it's coded samples and identified samples. I have to read "unlinked" again before I'm sure of myself, but the point is in general--I feel really quite comfortable with the regulations myself. I don't think that that's where the problem is or the issues are for us to address. I think the presumption that in these cases you go back for informed consent, which is where the--my understanding of where the federal regulations are is essentially sound. That's my own sense.

DR. GREIDER: I think that the issue comes to exactly what we were discussing this morning, and exactly your ambiguity is what is an unlinked sample. And I agree with what you just said, that I'm happy with the regulations as they currently are for these other categories, but we get into these situations with the ambiguity of when somebody says something is unlinked, is it truly unlined or not. And as I understand, the concerns are now that people are sometimes putting things in one category or the other based on convenience and that it's not really covered by current regs.

DR. COX: Actually, I think it is covered by current regs. It's just that because people know it's covered by current regs, they have a cat and they call it a dog, so if it's linked—if you can know what the identifiers are--then, that's coded or it's identified. It's not unlinked? So, by using these terms—if people were precise--and that's why I'm so keen on the terms, because the obfuscation has come about by not being precise in those definitions. The regs are crystal clear about this because--in my view. I agree with you, Harold. I think the regs are fine, but the way it's being--they're applied is not transparent.

DR. SHAPIRO: The area I need help with the unlinking. When I first said three of the four--it's actually what I meant now that I've read it again. I still mean three of the four for what I was saying because I'm trying in my own mind I find myself easiest with the idea that if you can go back--if it's possible to go back--whether it's easy or hard doesn't make a difference in the regulations. That's my--not the regulations I would prefer, not--so, I would three of the four but there may be real differences here.

DR. COX: But unlinked by the definition that we have it written now is that the--and this is a bone of contention. I don't mean to say that this is really simple. But unlinked means that for all practical purposes--.

DR. SHAPIRO: It's very hard to go back is what it means. Not that it's impossible, but it's hard.

DR. MURRAY: Okay. I got a lot of people looking urgent. I want to--Arturo's been patient. Let me bring him in. Carol, and Alta.

DR. BRITO: Just a very quick comment. When I originally read this, and based on the discussions we have in the past, I interpret this to mean that it would be very difficult—if not impossible—to go back, so there's two categories--major categories. There's unidentifiable samples, which are the ones that identified, and there's identifiable or potential to be identified samples.

DR. MURRAY: Got the three subcategories.

DR. BRITO: Not to belabor the point, but I think it's important to divide it into small subcategories as it stands and maybe say that he has a slight possibility of identifying those. But I think because of the way investigators will read into things, I think it's better to be very specific about what we mean and say, you know, very difficult but not impossible. When I read this, unlinked samples to me meant that it's unlinked but there's a slight possibility to go back and identify it, so it is identifiable.

DR. MURRAY: Well, we have--we have--I mean, we have been hung on this since the beginning. I mean, in a sense no tissue sample is totally unlinkable because you could always do a genetic fingerprint from it. If you can get samples you can go back, right? So, there is no such thing. By what--by that--my understanding, there's no such thing as a completely, in principle, unlinkable genetic sample. You give me tissue and give me enough resources, I can find out where the tissue came from. In reality, not that's going to happen in the foreseeable, but not as any kind of regular thing. The question is, in my mind, and I actually think the distinction is one very much worth maintaining between those samples which it is not reasonable to suppose can--identity can be established because we just--(a) we don't provide an identifier and (b) the context of the information we send forward doesn't give enough information to readily recover identity. That doesn't mean that you can't hire a private detective and spend \$200,000 and five years and figure out who it is. That's--that may be a possibility, but I think it's worth distinguishing between those things where in reality, it's not going to happen. You can be pretty confident that the identity of the person will not be reestablished, and where you send it forward retaining a code where identity could be readily reestablished under certain circumstances.

DR. BRITO: Like I was saying, I agree with that. I agree that the distinction should be made.

DR. GREIDER: I mean, I think we do get into some confusion here because I thought that I was agreeing with what Harold said, and yet Harold thought that I was disagreeing with him. I was agreeing with him what Harold said; I was also agreeing with what David said, which is if the last three categories unlinked samples, coded samples, and identified samples really are treated as the same and are covered by the current regs, then I'm happy with it. However, I feel that that is not how--what is happening. I agree with what Dave had said, that because there is this current way of saying you take off the identifiers and it is now unidentified that you get into some sticky questions about the--how are those actually removed, and do people go forward? Are those unidentified, or are they unlinked? So, there is a huge lack of clarity in the current use of this, that I feel that's where we need to do some work is to clarify that situation.

DR. MURRAY: Larry, Alta, Kathi.

DR. MIKE: Two points. Again, I think we need to talk about general rules and that there are always exceptions to the general rules and that that can be directives through IRBs about which areas that they need to look up with a special scrutiny, like the example of the 50. So, I think

we need to stick to general rules rather than getting a very specific--.

The other part which we have not discussed but I assume that we all agree that is this introduction of the idea of minimal risk, and are we in agreement with what Dr. Hook was saying was that any of these areas is beyond minimal risk and they're subject to this so that there is not another threshold of decision to be made about what is minimal risk when not in a genetic area.

PROF. CHARO: I want to, because I think I designated myself as the "reg head" on this table, I want to go back to what the current working rules are as best as we can figure them out and suggest that we use those for the moment. Now, the working rules, which you can find by taking a look at the definition of human subject, which is what helps us figure out whether or not we've got to go through the whole rigamarole of the IRB review and the possibility of consent requirements, etc. That human subject requirement focuses on the notion that you've got a living individual about whom the research is yielding identifiable, private information. We have seen here that "identifiable" does exist along a spectrum when you analyze it closely. We've also seen that in practice--and I know that the director of the office that's probably most important in interpreting these regs is here and I'm going to count on him to correct me if I get it wrong, as long as he's allowed to--the working operational definition of "identifiable" has been very straightforward. If there is anything, any kind of code, that links the medical record to the tissue--no matter who has it, no matter how many safeguards against its being used--that counts as identifiable. If there's no such code, then it counts as unidentifiable, even though we all understand that there are times when the cell size in your research means that you'll be yielding results that could tell you things about all the people in that cell, whether it's 4 people or 50 people or 500, and that one can extract probabilistic information, like that person has a 50 percent chance of having a particular trait because 50 percent of the people on the cell had it. But we act as if that counts as unidentifiable under the current regulations, we act as if there is no human subject around. Now, maybe we shouldn't be doing that. That is obviously an area where we could be working on recommendations, but I think it's worth understanding that, for the moment, the operating definition here is that unless you can individualize the information, you don't consider it to be identifiable. The fact that you've identified a probabilistic piece of information about people in a cell does not count as personally identifiable, and that gives us a kind of binary cut, which we can start with.

DR. MURRAY: What a clarification, Alta. This--as you understand it, and if Sherry wishes to speak this is fine, too--this goes to the sample, whether the sample is identifiable or not--not whether the material in storage is identifiable or not, correct? I'm asking whether that's how the regs are--.

PROF. CHARO: I'm not sure I understand how to answer the question because I don't think the regulations--as I read them and I'm begging Gary to stand up and take me off the spot now--I don't see them as operating on this kind of distinction you have here. They are always--they're always used in the context of a particular protocol.

MR. HOLTZMAN: That's at the level of sample.

PROF. CAPRON: These are rules that apply to an investigator who “obtains” individually identifiable information.

PROF. CHARO: I never understood the distinction you were trying to make there, but I do understand the regs. We just operate on different things.

DR. MURRAY: You don’t understand the distinction? It’s a--this is important, because that’s a fundamental distinction in the report, and that is what’s in the repository--okay?--that the steward of the tissues holds, and what is, goes in, what is involved in the protocol, what goes forward to the hands of the researcher. That’s a fundamental distinction.

PROF. CAPRON: And that distinction is in the present Federal regulations. It is because by implication there will be not just tissues, but data sets where you--the question is, to use the language, “Human subject” means a living individual about whom the investigator conducting research obtains and then one category is identifiable private information, which is explained--and I mean private information must be an individually identifiable, etc. So, that means if that person doesn’t obtain it in an identifiable fashion--.

PROF. CHARO: I do not want to encourage you to go forward, and I do not want you take it as if I don’t understand this report. The fact that I don’t share the--there are certain things I don’t share that are not important to the rest of the discussion. The point simply is that we don’t need to be puzzled about this little category “unlinked.” “Unlinked” as it was used in these definitions was supposed to be about the situation discussed this morning in which no identifiers, no codes, no--everything was stripped, and yet you had cell size of 50 and you could go back to all 50 people and say, “Probabilistically, you were a member of a community that had certain findings about it.” All I’m saying is that my understanding of the regs--please correct me if I’m wrong--is that that doesn’t count as “identifiable” under current interpretation, and therefore we can choose whether or not to do something about that.

DR. MURRAY: Thank you, Alta. Carol...

DR. GREIDER: If you have 50 individuals where you’ve sent material forward to a researcher and they keep the information on who those 50 people are, I don’t think that is unlinked. Somebody has the codes. You just said “no codes.”

PROF. CAPRON: You sent the following 50 samples to...I don’t know if it’s sample A, if it was one of these 50.

DR. GREIDER: That’s a code to me. All but 100,000 samples in your repository and you know that these 50 went to those people. There’s a code to tell you...

PROF. CHARO: You may be right that is a form of coding, and you are certainly right that it is a degree of identifiability.

DR. GREIDER: That identifiability is going to put you into the realm of dealing with a human subject. So all this is is a descriptive piece of information about how the current rules operate. We are free to say that we think the current rules are too lax, or that I’d change everything

that I've said if that's the interpretation on my way of viewing the world is that if you have 50 samples and you can find out who those 50 samples are, then that's a code. And so, that's what I'm just saying about believing the current regs. I understood that those would have been covered. Right. So, it's just that I disagree that with the current regs. Okay.

DR. MURRAY: Okay. Okay, good. I think we got some clarity there.

DR. DUMAS: Let's put it down. Let's write it down.

DR. MURRAY: Kathi has been patiently waiting to say something. Do you still wish to speak, Kathi?

DR. HANNA: Yes, I'm just -- I just wanted to suggest that one of the reasons I think why you've separated out the samples into four categories, although it was never articulated, I think it's because the subtleties among those categories place a different focus or responsibility on a different person or group. In some cases, I think the responsibility lies more on the repository. In some cases, it lies directly on the investigator and I think it changes the consent process. So, I think that the four categories were separated out because there were so many subtleties having to do with what people were told and what the repository's responsibilities were, and what the IRB's review process should include. And so, I would urge you to move from those four categories into the process issues, and how each one of those categories would be considered through the existing regulations and the process in place. I think that's the only way you're going to get to a recommendation.

DR. MURRAY: Let me try to rephrase a recommendation, possible recommendation, for the categories of unidentified samples and unlinked samples. And let's make it -- recognizing Carol's concern, we're talking about -- let's just put that in -- not eliminate it, put it aside for a moment. Say this is genuinely unlinked, and I mean unlinked in two ways: (1) there is no code; (2) there is no reasonable prospect of figuring out who that was, even as part of a relatively small group. Okay. Let's say that. Do we agree that that research -- am I right, Alta, in thinking that the current regs say that that doesn't count as a human subject?

PROF. CHARO: That's right. The implications being no IRB review; and, of course, therefore, no consent issues.

DR. MURRAY: Okay. Are we content with that as a practical policy, that we would recommend?

DR. COX: I'm very content with that, personally. You can't go back and find out, okay, who somebody is because there is no code, and I'm happy with that.

DR. SHAPIRO: Can I just -- I'm willing to give way on this, because I don't think that my opinion is so well formed. But let me -- the example I think is very interesting. Because, even though, with the list case, you cannot go back to a single person in the sense that nothing you have in hand, any material, can be identified with any individual. If you think about that as just the beginning and end of it, then you might as well collapse these categories. But that's not the beginning

of it, if I understand it correctly. Because if you decide to go back and try to recontact and recontact the group, as you would require, as I understand it, but you would go ahead. That by itself generates information to an individual which may require some thinking, because that might --some harms could improve. Now, it's that that has me --maybe it's just a small issue, which is not deserving of any --

MR. HOLTZMAN: But Harold, I think it's important for you to remember what I think you've heard here, and what I believe is the case. I did a preliminary work on these 60 samples and got some information that said, I really would like to do study on these 60. You don't go back to those people with the results of your study. You go back and you say, "Would you like to participate in the study?" That piece of information you've got in your initial study is really not logically different in my mind. And even if you'd never done a study, if you'd gone to the hospital, you've done a look at records or the pathologist and said, "Do you want to do a research project? Here are 60 people that would be interesting for that research project. Now go out and consent them."

DR. COX: I think the point that you're making is a concerned one, and I would like to say is that --and I hate to ever disagree with Alta. But for me a code is a code, and what Carol said is what I believe. Now, I don't disagree with Alta in terms of what the regs say. If that's what they say, that's what they say. But I actually don't think that's what they say, because a code is a code. Now, if they allow you to take 18,000 people and to go back and subdivide them, so you can see what those 50 people are. And even if you don't know those people's names, what you are saying, Harold, is what I agree. That puts those 50 people at greater risk, because it makes it much easier to go back and get them. Now, my view is that "unlinked and uncoded" means just that. When somebody gives you the samples, you don't know who the hell those people are. If somebody keeps track, even if the group of a subset, if it's a whole group of a large number of individuals, then that's fine. Now, you say, "Well, this gets very sloppy right now. Because what's too big a group? Is 50 small enough? Is 2,000 big enough?" So, I think in your [Dr. Hook's] presentation to us, it's brought this idea up that I had never really considered before, which is that if you have a group, okay, how small a group is it? This is why, as much as I hate to admit it, I think that Alta's interpretation of the regs is probably right, but it makes me very uncomfortable for the same reason that you're saying, Harold. So if the regs are right, that you can take these different groups and they're anonymous -- I mean they fit into the regs, then I'm troubled with the regs right now. Because, as you pointed out, Harold, they collapse.

DR. MESLIN: There is good summarizing. We're trying to move towards recommendations. And what Alta has said is correct, in terms of how the regulations operate. And if there is a feeling that the Commissioners have --that the interpretation or the operationalization of those existing regulations do not satisfy their own views, then I see a type of recommendation you'd like the staff to work on. And that recommendation relates to the mapping between what the regulations say, with respect to unlinked or linked samples, and whether you would like to recommend a guidance to OPRR, or a regulatory change, or educational change, or some other such maneuver that allows the Commission to feel comfortable, that what the regs say and what it wants to say in advising others about that reg is clear, and I think we can do that. And I don't mean to

sound short in making that, but I'm --I hear a recommendation.

DR. COX: I make that recommendation, particularly, in this context of the 50 samples that we talked about in your presentation. What are the regs with respect to those 50 samples? And if those are viewed as not covered by the Federal regulations, then I want to deal with that because I'm uncomfortable with that.

DR. MESLIN: And I also hear a case, which is what Carol asked for. She wanted a specific case that relates to a recommendation that we might have. We now have a triangulation.

DR. HANNA: Can I just ask a brief question here? And, that is, in the case that we're talking about, once those people move out of the unidentified status into the --now, they have become identifiable. Doesn't that immediately put them back into the regulatory framework? We have talked about the fact that some of these categories were fluid, and people might move from one to another, depending on what their research reveals. And so, it is entirely possible that somebody starts out in one category, but moves into another one. And once they move into the identified, or identifiable category, does it change?

PROF. CAPRON: If you're going to go contact them, then, obviously, they are now research subjects. The issue that was so well posed, I thought Steve's example. Let me just ask the geneticist, and physicians, pathologists in the group. Would it be fairly standard practice that pathologist sending off 50 samples to someone who says, "I want to do research on a gene for prostate cancer or something," would know which 50 samples, even if they weren't coded. Here is your 50 samples. The answer is, yes, that would be standard practice. So, this "unlinked" category is going to be a major --it's going to be the default position, except when you actually do code. So it's a very important thing to get it right. Now, I thought Steve's analysis was very good in principle, that you're only the research subject when once we say, "Now we want to actually do the study on you. All we found out is something interesting and provocative." We could, therefore, limit ourselves to giving guidance to the IRB. The kinds of thing you should be concerned with is that the sample size is so small that any finding about anybody in this group is going to, in some sense, be identifiable data and you want to set a lower limit that isn't too low to say, "No, if your sample is that small, we've got to treat this as human subject research, and it isn't totally exempt." That would be guidance in OPRR; or we could say --and this is where I gathered Carol --and I think David is now, although I think David's position is changed.

DR. COX: No, my position has been the same. My interpretation of the regs is being put into question.

PROF. CAPRON: Well, okay. The question is do we want to recommend a change in the regs? And the issue is it seems to be very different with two models are what you're going to find. If you find 50 percent of the people in the group in fact have the gene of interest, and there is nothing special about these 50 samples, then I think Steve's analysis is basically correct. And you're going to go to those people; or, in fact, you don't really care if it's those people, just contact a bunch more people and say, "We want to find out if there is some correlation between this preliminary

finding. We don't know if it was you who had the finding, or whatever." What really is unusual, or what is very different is when you've done this with 50, and 50, and 50, and finally find one, and now you very much, you say, "I really want to get that needle in the haystack and really know a lot about him." And, clearly, at that point, you've got research, but you've also created a very different situation, if you've got a very sensitive gene. I mean this is the gene for proclivity to developing every disease in the world. And you know as one of these 50 people, really all 50 of those people. It's not a very neutral statement if you say that, "Well, we have something to look at. We'd like to talk to you. You want every one of those people." And, basically, if that's the situation, which you probably cannot predict in advance in some of these studies, then, potentially, that linkage becomes the kind of thing where you would think people would want to know that they're subject to that before they get drawn in in the first place. And so, for that reason, I think I'm now with Harold, and Carol, and David in saying that we should differentiate; that we should say that unlinked samples, because of this risk, ought to be treated as initiating a research process. And they are different than being asked to be sent the medical record with all identifiers off, so you can see something else. Because it is for the moment the potential to find out something very different about the person in that situation. It seems to me that I am, therefore, with Carol and David.

DR. MURRAY: Actually, I was following you till near the end, but Carol had a point of clarification.

DR. GREIDER: If I understand it, we're talking about the difference here is no IRB review, and IRB review which could be either expedited, or a variety of other things. So, we're talking about are you even going to be considered by an IRB. And we're thinking of maybe moving it to -- okay. It might be expedited review. And it seems to me that that is not a huge hurdle that we're raising to get you into an IRB under possible expedited review.

DR. MURRAY: But would it be something like this, where there is some possible -- because even if there is no personal identifying information, or there is some possibility or prospect that the person would be recontacted as a result of this research, because a list of all participants has been retained, or could otherwise be, that we would recommend a change then in the regs to at least some form of review by the IRB. Is that where you're headed?

PROF. CAPRON: Yes. And it's because, in a sense, even with a group of 50, you are, in effect, finding out something that is identifiable with that person as a member of that group of 50.

DR. MURRAY: Which puts them at risk of being recontacted. Now, suppose I give you the 50 and the 500 samples -- 50 samples, but I don't keep a list of who I gave you? Now, that wouldn't happen at Mayo. It may happen in another context, but -- it may happen at Mayo?

DR. HOOK: It could potentially happen. I just -- the question was posed to me this morning was: If you had taken a cohort of 50 individuals, and this has been approved by the IRB, so that you now have an IRB number attached to anything that happens to that patient's record. You have made the linkage there. They can go back and tell, because it has gone through the IRB process. Even if it was expedited review, you have that potential linkage there. That's what we're talking

about. But I don't know that we have to be thinking in a threshold — a dozen, or 50, or 500.

PROF. CAPRON: No, we don't have to take this approach. That was if you were taking the other approach and saying, "Unlinked, we'd just give guidance. Don't let the number get too small, because then it becomes really identifiable." Suppose you're doing research on violence, and you had already a sample of a number of -- DNA from a number of violent criminals.

DR. MURRAY: A nice, uncontroversial example.

PROF. CAPRON: And one of the DNAs was from a sample taken from a victim of strangling. And there had been a rash of stranglings in the city, and the Case Western Reserve strangler had never been found, and here in this sample of 50 you've got it. There's the match. It isn't just to find a set of genes that you believe is linked with violence, you have the match. At that point, every one of those 50 people is a suspect in multiple murder.

DR. GREIDER: However, you've got all kinds all kinds of other regulations that are going to be imposed.

PROF. CAPRON: We won't use that example.

DR. MURRAY: Alta, and Larry's been -- did you still want to -- we have deviated from the list horribly, and I apologize. Alta and Larry.

PROF. CHARO: You know, as somebody who has argued in favor of stronger protections to human subjects and most other contexts, I find it interesting that I am arguing against the pull now toward a tightening up on the regs, and it's for several reasons. First, I've not been persuaded that the urge to recontact all people in the cell, in order to ask them if they're willing to now individualize their samples and have them examined, is likely to happen all that frequently. Second, we heard outlined by Dr. Hook, an intervention that makes this scenario not only less likely, but more benign in the rare cases where it happens; and, that is, in the way in which the repository, which is the keeper of this list of all of the people in the cell interacts with those 50 or 500. The letter that they get does not, in fact, have to represent anything that tells them much at all, if anything. And the letter is controlled by the repository, not by the investigator, who is all hot-to-trot to find the needle in the haystack. The letter is controlled by the repository, which most of the time will be different than the investigator, although on occasion not, and on other occasions, it will be within the same institutions. There will be institutional pressures. I grant all of those things. Third, if we were to go down this road and essentially to say that the notion of identifiability that underlies the definition of human subject is now going to be expanded to include not only individual precise identification, but probabilistic identification. I think we've actually opened up a much wider area of concern about the way in which we conduct human subjects research, and what would now have to go to IRBs and what wouldn't, unless we're going to somehow specifically limit it to genetics protocols, which will get us into the muddy waters of what is genetics. Because nobody here is sitting around thinking about the implications of this redefinition of identifiability in probabilistic terms for all of the other areas of surveying epidemiological research, where it could have applicability. So, there is a kind of -- there is a kind of messy regulatory issue to be dealt with down the road, if we continue down this

path. I'm not convinced it's actually as frequent or as difficult to solve with other methodologies as we've been imagining. And, finally, we are perfectly free to make recommendations that are aimed at repositories, in particular, whether or not they are repositories that exist within an IRB jurisdiction. We can aim them at repositories, and at the professional societies that deal with repositories, and those who in fact funnel things through repositories, saying, "We've identified this as a problem that may occur in the future." And we would love to see you have a kind of professional standard for recontact of cohorts in which, on an individually unidentifiable basis, one or more members have been identified as having a trait of interest, such that investigators want to recontact. Let's have a style of recontact that is not alarmist, does not in fact raise the issues of psychosocial harm that concern us, and in this way kind of slither by the need to work on the messy issue of reforming the definition of human subject. And, remember, by the way, one last thing -- I apologize. The IRB system works through a great deal of self-regulation. And the first moment of self-regulation is when a PI recognizes in herself that she has to go to the IRB. That's one of the weak links in this system indeed. Because often they don't recognize that, and if their department chairs aren't really on top of that, they don't go. Now, anything less than a bright line that tells them when to go and when not, is going to be nightmarish. So, anything that tells them when you think that this may turn out to be a cohort in which probabilistic information is going to be developed, you probably should go to your IRB, because now it probably is a human subject. This is going to be very, very hard. So, they either have to go for every kind of tissue research. So, we're now putting everything in the IRBs, or I think we want to maintain apparent distinctions.

DR. MURRAY: Larry and Carol. I have to note an irony, as I think --I think it was Alta who first brought this sort of scenario to our attention.

DR. MIKE: Yeah. In our previous discussion, what was missing was Alta's analysis about what --how the current system will deal with it. I think that's made it real clear to us about -- to about our specificity or recommendations. But let me make one --a specific distinction here. One is that we're talking about --in principle, we're talking about a simple division between identifiable and unidentifiable. It's in the operations that we are making the finer distinction among the four categories that we're dealing with. So, I don't think we're at odds when we say some of us prefer a dichotomy, and the others of us prefer this more specific language that the researchers use. I also agree with Alta. I think I'm agreeing with you. Sometimes, I'm getting lost in the trees here again. But I'm not convinced that we need to change the regs. They are not set in stone, and I think you can always get some flexibility. So, I think some advisories about what areas that one must pay particular attention to, and not make it a change in the rules, would suffice in dealing in any of these areas.

DR. GREIDER: I'd like to agree with Alta, and I would with you, if I could believe the one statement you made, which is the letter that's going to go out to these 50 people is controlled by the repository — as in the case that we heard this morning, where the letter would be controlled by the repository, because that's the mechanism they have set up at the Mayo Clinic. And I think that's perfectly fine and a very good way to deal with it. But I'm not convinced that that is going to occur in most cases. As we learned looking at the different kinds of repositories that are around,

some of them are very informal. They are not a big, large operation like the Mayo Clinic. It's four or five people getting together, and asking their local surgeons to give them material. And in that case, I'm not convinced that the letter is going to be controlled by the repository, as opposed to controlled by the researcher. And so, that's where I have a little bit more trouble with your assertion that the letter is going to be a well-formulated letter, that's going to come from the repository, not by the hot-to-trot investigators.

PROF. CHARO: Do you think the hot-to-trot investigator will write a letter and say to the repository, "Please send it to the 50 people on the list."

DR. GREIDER: Because there isn't a repository. There is five or six people that got together --it's a couple of pathologists. I mean in a lot of cases, this is how some research is done. So, if your assertion were true, that the letter is controlled by the repository, and done in a very straightforward, uniform way, then I would agree with you. I don't have the data to say how frequent these different things occur.

DR. MURRAY: Harold and David.

DR. SHAPIRO: There is a very practical problem, I'm persuaded on; that is, if we can accomplish most of our objectives, providing the appropriate protections, within the existing regulations there is a very big plus to that for all of the reasons Alta hasn't talked about. So, now, as a matter of principle, I'm unpersuaded that -- just to take this example -- that that, therefore, saves people from some harm. I would like to actually protect people from that. I am persuaded or willing to be persuaded that we could achieve most of that objective through guidance, there's a lot to recommend that. So, one way of going at this is to say, "Look, let's work out these -- try to get as far as we can with their ideas within the existing regulations." I had actually misread the existing regulations. I would have thought that this fell within them, but they don't, and I accept your interpretation. So that --but I think they're just for purely practical reasons, if we can achieve a very high percentage for our objectives, that's very worthy, and maybe, Tom, my suggestion is that we take that and say, "All right. Let's write it that way, where we can't change the regs. Let's give guidance, and see if it gets us there or not."

DR. MURRAY: Then why don't we keep that, in fact, as a kind of framework for the rest of today's discussion to see to what extent can we work within the existing regulations by bolstering interpretations, providing guidance points to consider whatever we can?

DR. SHAPIRO: I think actually we can achieve most of our objectives that way. That's --but I could be -- I suppose I could be persuaded otherwise.

DR. COX: You took the words out of my mouth, Harold. I completely agree with what you said. I, clearly, have misread the regs. I hate it when I'm wrong.

DR. SHAPIRO: Don't worry. I'm used to it.

DR. COX: I think guidance is the name of the game here, and to take the situations that are confusing, and to shine the light on them, in terms of guidance, to say we recognize this, and

but that there is a way of dealing with it. But I'm not, for one, in the position of wanting to change the regs right now, because I do believe that although --I believe exactly what I said. I won't say -- I completely agree with what you said.

PROF. CAPRON: How do we deal with Alta's problem of a trigger for the review, the either --a bright line, which we can expect investigators to learn, or a fuzzy line with five qualifiers and criteria, which they are less likely to learn, and, therefore, less likely to apply the way that idealized model, do you suppose?

PROF. CHARO: Well, the bright line exists now. If they receive a coded sample, they are doing human subjects research, have to go to the IRB. That's the bright line now.

PROF. CAPRON: Right, but the question is if we think that unlinked -- I mean I take the Chairman's statement to be along the line of the first of the two alternatives and I was suggesting that it's a matter of guidance. We say the sample is small, if the contact letter is going to come from the investigator, perhaps, than from the --these are the kinds of reasons you could say, "No, this needs to get reviewed." But if it's on the other side, then it's a matter of helping to make sure it gets designed correctly. But you may trigger questions.

PROF. CHARO: If you want to pursue this avenue there is a bright line trigger you can select, but it's a little harder. If an investigator receives an uncoded sample from a repository that's maintaining a list of all of the samples that were delivered, the investigator has to go to the IRB. That would bring this in to IRB review. It's a little harder for the investigator, because they got to now inquire about the repository's practices, and they're going to have a conversation. But I suspect it's going to be a little confusing from time to time, but it will get normalized. It requires that the IRB and that institution have voluntarily taken on a wider jurisdiction. In fact, I'm not --what I'm confused about on a legalistic level is whether they're allowed to take that on, because it goes beyond what the legislation and the regulations authorize. They are allowed to have additional protections for human subjects, I don't know about their legal authority to expand what constitutes a human subject. Because that's the kind of invitation to ultimate expansion of their jurisdiction.

PROF. CAPRON: What stops them? Their jurisdiction rests with the institution. The institution can say, "We want non-federally funded. We want everything having to do with any living being."

PROF. CHARO: It's true. An institution could say, "We want research on dust mites to go to the IRB." And so -- so, they can say, that even though this doesn't meet the definition of human subjects, we --the institution would have to voluntarily decide, and this would be --if you wanted to pursue this, this would probably be your best new bright line. It's going to bring in research that never in a million years would generate the kind of recontacts that you're worried about, and it would mean the IRB would have to go through each one of these requests for samples.

DR. MURRAY: It could be, but it could be one of these expedited --

PROF. CHARO: Expedited reviews.

PROF. CHARO: That's right. But it's --let me understand what it is that you're suggesting. And it would leave each IRB struggling to figure out how to explain to everybody in the institution which sample --samples research has to go in, and which doesn't. Is it only in genetics? Is it any sample? What constitutes a sample? I mean each one would struggle with that to communicate to their own PIs.

DR. MURRAY: I like though, Alta, that I heard you actually suggest a possible alternative, a sensitive point, where we could influence policy; and, that is, that the --we have used different terms. But since in the steward of the human biological materials, right -- rather than necessarily folding it? I mean these --would both be done, or they might be alternative. Rather than folding it into the IRB, instead say to these --say to whoever manages or collects, if you have -- our recommendation is that you develop as a professional standard. If you have this sort of possibility by keeping the list, even though the samples go out. We recommend that these points be considered, blah, blah, blah, about certain --you be the control point for access, if there should be any request for the access.

PROF. CHARO: All right. This addresses Carol's point about how realistic that is and -- oh, sure.

DR. MURRAY: Which do you think is better, both the IRB, the steward of the --

PROF. CAPRON: Well, the IRB could say to the repository, "Before you send out samples make it clear to the group that you're sending it to that any good contact can be done by our specifications."

DR. GREIDER: But an IRB is a recognized entity, and a repository is not a recognized entity under the current regs, right?

PROF. CHARO: You know, personally, I think until I understood better the competing interests, what's the likelihood of these scenarios occurring? Why is it, and, perhaps, actually, Dr. Hook can talk to this. Why is it that it is important to keep a list of those samples that you sent out, rather than destroying that list? It would be easier to make this judgment call. My instinct always is to not rock a boat that's still floating, which is why I've been resistant to the idea of tinkering with the notion of human subject, and have preferred a kind of educational route aimed at PIs, repositories, however, informally to find, etc., for professional standards of behavior. And also, because IRB workloads are already so excessive, compared to the amount of time, and, certainly, remuneration that's offered in exchange for the service, that one wants to add to the workload with some degree of discretion. And this is potentially a fairly large workload. No matter even if it's expedited review, it's a large workload to even just go through these to find out what the likelihood of a recontact scenario might be. Maybe you could speak to why it is that you prefer to keep a list of the people's identities, whose samples were being sent out without any codes attached, what advantage that serves for your purposes?

DR. HOOK: Primarily, just internal documentation, more than anything else. Again, if a --from a practical purpose, it can be blinded so that the investigator himself or herself wouldn't

necessarily have any access to that. The scenario that came up though causes me to think in a different way than I had before, in that, when if, at some point, there is a link established between given patient history, their specimen, and a given IRB protocol, there will be a record maintaining that, even if you know other records are destroyed. Now, if you have a specimen, literally, that has been collected, and has never had an identifier associated with it, that will remain anonymous. There is no way that that can be linked in any possible way. If it was just a situation where there has been some previous linkage, even though as of left the institution, it was anonymized at that point. And then we have re-entry back. Because there was, at some point, a linkage established. And that's the specific dilemma.

PROF. CHARO: And the question is: What would happen if the direction of our discussions was to lead all of those who have stored samples — stored materials — to begin to change their practices, and to release samples without keeping any note of which samples have been released, specifically because they want to avoid this scenario from occurring. You said that from the point of view of those tissue banks or repositories, that it interferes with internal documentation, for whose purpose I'm not familiar with, and that's exactly what I'm asking, to the extent that people here seem upset by even the remote possibility of these scenarios of future, probabilistic information yielding recontact, it's good to know why one maintains even a list of those samples that have been used -- those materials that have been used to make samples.

DR. HOOK: You don't have to necessarily. In other words, if prospectively everyone agrees, "I'm going to take this specimen, and as soon as it leaves the phlebotomy site we'll no longer know who it ever belonged to," that's quite possible to do. That's quite possible that we could do, and there will be no linkage necessarily established.

PROF. CAPRON: Alta's question is, why? And your answer was, "Well, it aids record keeping." Well, it is record keeping. So, why do you want to record keep that way. I wondered if it was because the research will call up and say, "Could you send me another batch of those same 50?" Because I just used them up, or my freezer went off, or I want to continue my research on those 50, and I don't have them anymore. He would say, "I don't know which 50 I sent you." Oh, gee, I found out a lot about these, and I'd like to get them again. Is that a reason, or is it?

DR. HOOK: Because they can do that easily, Alex. I mean they're just --they keep one in the repository unidentified, just as that group of 50. So, it's the possibility of going back to the record. And for me you know this is a very good question.

PROF. CAPRON: That's what raises the question. If you keep them as an identifiable group of 50....

DR. MURRAY: Our esteemed Chair has -- I said it with no hint of irony. Our esteemed Chair has suggested this might be it. We've had a good discussion about this. I think we're clear on some things. We may disagree about some things. But this is an appropriate time in which we instruct the staff to prepare for us a few options as to how we might respond to this. Right? One

option being no change in the regs, guidance, whatever. But in further conversation, we're going to ask the staff to come back and see if they can give us some creative suggestions. Because to put them out, and then we'll expect each of the commissioners to come back and say which we think works. Is that all right?

PROF. CAPRON: Could we see if staff has any means of gather an answer to the questions that Alta was asking, which is, why this is -- is this the practice? And, if so, why? What would be lost? Because I think part of your question -- one recommendation -- would be don't do it that way. Don't keep track.

DR. MURRAY: If, in fact, almost nobody does it, nobody feels they're giving up anything by not keeping the rest of it.

PROF. CAPRON: Or if a lot of people do what they say, yeah, but we don't have to.

DR. MURRAY: Well, you don't need a formal survey, but we need a good sounding of repositories. All right?

DR. MESLIN: Just raise the question, so that staff can provide you with exactly what you want. And what exactly do you want?

PROF. CAPRON: Do most repositories who may send out samples on an unlabeled basis keep information which would allow them to say which are --secondly, why do they need to adapt? And, third, what would be lost if our advice to them was don't do that, that it would better if things were truly unlinked, even to the point of... And it might be that some of those groups that told us the policies, and whatever.

DR. MURRAY: Elisa, would you be able to help us figure out which groups to ask? Thank you. All right. That's very helpful. We're going to go on now. There is a category --I think I know the answer to this, but I'm not sure of anything at this point. Do we agree that when samples go forward with identifiers -- now, I'm talking about express identifiers, names, Social Security numbers, whatever, something where it's clear that the --as the sample in the hands of the researcher would permit the identification of the subject, that that requires informed consent -- informed consent. Is that agreed? IRB review, is there any disagreement about that?

PROF. CHARO: Only to the extent that the consent can always be waived if it meets the criteria for the waiver of consent.

DR. MURRAY: Which would be?

PROF. CHARO: Minimal risks, impractical to reach these people, doesn't affect rights and welfare, and number four. What's behind door number four?

PROF. CAPRON: Pertinent information be provided to the subjects later.

PROF. CHARO: Thank you.

DR. MESLIN: Okay, that's fine. So, the language of the current regs, or identifiable

samples, we think that's still a good idea. Is that correct? Everybody agrees with that? And the agreement was with relation to consent, or that it is reviewable, and it's --are you making the recommendation with respect to consent issues, or IRB review? Is it for developing categories of recommendations? It would be nice to say that case is something that is within the domain of IRB review, in which case, the regs kick in and tell you whether or not certain procedures would kick it back it our, or expedite, or waive consent procedures, or the like. It's just --

PROF. CHARO: I gathered your intent was to say that when the name and address, social security number, birthmarks are there in front of the researcher, we all agree that the current regs operate just fine. It has for the IRB review, and that the regs provide the appropriate out for a waiver of consent on rare occasions.

DR. MIIKE: I only raise the issue about a minimal risk issue, minimal risk, and are we going where the differentiation, or are we going -- my understanding from Dr. Hook was anything was beyond minimal risk.

DR. HOOK: As a data finding.

PROF. CHARO: We haven't talked about that.

DR. HOOK: Ipso facto minimal risk, if it's genetic research with an identifier. It would not satisfy the --

PROF. CHARO: That's their definition. We have yet to discuss whether or not we would like to flush out the meaning of minimal risk and say we have a view for this that we'd like to share with the IRBs around the country.

DR. MURRAY: I think we understand that's the view that IRB has taken. We haven't made a call as to whether we would agree with that.

DR. SHAPIRO: I think Larry and --Larry you're asking we ought to consider this directly? If it's genetic research, it's automatically above minimal risk.

DR. MIIKE: Yeah, that was a --because the regs --all I'm saying is that are we going to take that position, or are we going to give the IRB the option of deciding when there is or is not?

DR. COX: So, I was --I found Dr. Hook's presentation very compelling in many ways, actually, I must say. I would like to err on the side of being conservative and say that genetic research is beyond minimal risk for exactly the arguments that he made.

DR. MURRAY: Is this the conversation we're going to have right now? Steve Holtzman's body language suggests no.

MR. HOLTZMAN: Are we going to split genetic research up with everything else? And you can distinguish, whether you're looking at Alzheimer's data versus the genetic basis of finger whirls, and is that above minimum risk? I mean we've been down this path nine months ago. In your institution, if I do a genetic study involving what is the genetic basis of whether I have whirls, as opposed to which is a single gene trait, as it turns out, is that minimal --above minimal risk?

DR. HOOK: We would review it, yes, in terms of your participation of being informed about other, perhaps, unanticipated identical information that may arise in genetic research, what impact it may have. The issue here is not so much to exclude genetic research as a separate category, and lump that with minimal risk. The idea was, we felt we needed to broaden the concept of minimal risk to include potential psychosocial harm. Beyond physical harm, the current regulations. And that could include Alzheimer's research in a variety of ways, as opposed to straight genetic analysis.

MR. HOLTZMAN: Because it is not triggered by it being a genetic analysis. It is triggered by looking at research protocol, and asking whether other harms that are not physical harms might result with an analysis of DNA, RNA, protein... looking at heritable traits. The issue is what is the nature of the research, what is the prospect for harm that could result?

DR. HOOK: And that was the overarching principle. Our statement and our policy was simply to say that the context in which genetic research would be performed, where identifiers were maintained, would essentially by nature fall under that larger identification.

PROF. CHARO: I think that these -- it is hard to not --to avoid discussing these issues together, although it's disorganized. Because the implication of a strong view that this area of research, genetics, is rarely, if ever, going to be minimal risk. Is, therefore, a statement that it is rarely or ever going to --rarely or never going to be possible to do this research without getting actual consent. So, they are very much linked. And I do think it's possible that we can offer some guidance on the notion of minimal risk that may build off what's done at Mayo, and may not be precisely what was done at Mayo, because in some ways it's about proxy language. The issue is genetics research, some of us would still claim has a kind of special resonance in the public's mind. I know Steve wouldn't necessarily share this, and that in the public's mind, it tends to be associated with things that are highly penetrant, highly determinative, which is part of the problem. But, in addition, it only becomes an issue when it's disease-related, or related to a socially significant characteristic, that genetic research on what Steve was saying during the break, whether or not earlobes are attached, or not attached, where genetics research even on your hair color may not, in fact, raise the kinds of psychosocial harms that the others do. That's one kind of additional nuance we might add that might yield a statement that's a little bit less categorical than Mayo may be. Right. And it opens up a wider door for consent waivers, depending upon whether or not the other exceptions --

DR. COX: It may not have those harms, Alta, but it might. And I take Steve's point, is that it doesn't have to, so --but, again, the words that you used, Dr. Hook, I thought really sort of addressed Steve's points quite nicely. The problem is if we're in this situation, if we say, "Well, genetics either is minimal risk or not," I mean that's what Larry's asking. He's basically asking for a straightforward answer. And, ultimately, that's what everybody is going to look for. Steve, I don't want to reopen this issue. You know I actually don't think that genetics inherently is different from any other kind of research. On the other hand, is that people ask for a straightforward answer, yes or no. And if I have to say yes or no, then I want the IRB to review it. So, I don't know how to get around the bind. I take your point very clearly.

DR. GREIDER: I hate to disagree with David, but I'm going to disagree with David,

and I agree with Steve; and, that is, that I think that we run the risk when we separate out and say it's just genetics that we're concerned about of walking down that path of genetic determinism. And so, I agree with -- now, I'm going to confuse who said what. But the idea that Steve promulgated, which was we should state very concisely what it is that we are concerned about and avoid putting the label "just genetics" on that — I think we all agree about what it is that are in the harms; that there are psychosocial harms and these sorts of things. If we can find a way to carve that out without stating specifically that it is genetics that is never a minimal risk, I would be a lot happier.

DR. MURRAY: But rough syllogism could look something like this. In line with the Mayo's position, risk of psychosocial harm ought to be considered as a sort of risk that might drive a thing --drive a protocol above the minimal risk level. That's the major one. The second premise is, genetic research may create certain kinds of risks — a certain kind of psychosocial harm — genetic research, as well as other kinds of research. Certain genetic research, certain research, right? Therefore, we should scrutinize any research that might cause such harms, including certain genetic. That's true -- is that it? Is that where we are?

PROF. CAPRON: The effect I do not think is as radical as Alta suggests, because your suggestion was this is going to preclude it. That's the first way out of requiring consent. But if the --if it's very difficult to contact, or if rights and welfare are not going to be adversely affected, and so forth, those are all additional reasons for you to say, "No, you actually do not have to have consent of the people who could be looked at, even though you are doing analysis which you have thought had a nonphysical harm." I mean the whole point in here, as the first part of your syllogism, is that there are nonphysical harms. If you are doing research on AIDS, the risk to you is not having a little bit of blood drawn. Okay. Any IRB that looked at this and said, "Of course, it's minimal risk. It's a little blood drop." It's what you're going to find out when you look at the blood. This is just the same kind of thing. Certain genetic inquiries will raise that, and all we're doing is flagging that IRB should take the approach --

PROF. CHARO: Genetic and other inquiries like AIDS.

PROF. CAPRON: That's another thing have --that the notion of harm obviously ought to include not -- this is not a new idea, it's been around in other context. It's just underlining --

DR. MURRAY: It seems --and it seems valuable though to state it in this.

MR. HOLTZMAN: And I believe OPRR has already written guidelines on this specific subject, or someone could add something, which I read some time, that said, "When you're doing certain kinds of research you need to be sensitive to a broader concept of what could be harms. This isn't written.

PROF. CHARO: The notion of risk --I'm sorry. It may be that we were miscommunicating, Alex. Because I never intended to say that we're --I think I said that it would be precluding anything. The notion of risk incorporates both the magnitude of the harm — which is where the need to recognize psychosocial harms is real — is pertinent. It also incorporates the likelihood of harm occurring. And this where the existence in a protocol of some planning on how

and when to recontact people, in light of results that have been found, now that you can backtrack, I think, becomes pertinent again. Like the existence of the genetics subcommittee that you have -- or advisory committee that you have there to modulate the interactions with people when they are being recontacted for further information, or to send information downstream, I think significantly reduces the overall risks. Because it reduces the probability of one of these psychosocial harms occurring. And I don't want us to lose track of that, and I think that is one place where we can make a contribution that goes beyond within the current regulatory guidance, which certainly does say that psychosocial harm should be considered. There is no lack of that, and the IRB handbook talks about it in some length in the context of kindred studies. Something that really begins to give IRBs ideas about how they constitute bodies that will help to reduce the risk of these harms occurring, and, thereby, more frequently render a protocol appropriately categorized as minimal risks is probably worth doing. It's a way to help them figure out how to accommodate patient or subject interests and PI interest simultaneously. The fact that some of this is minimal risk does not necessarily mean consent is going to be waived. That's going to depend on other threshold issues like, as long as it's easy to get consent you have to. But it's an important part of the overall equation. This is where I think we can do something that's different.

MR. HOLTZMAN: So, Alta, looking at the chart, if I understood what you said, is when one goes down to the box, would pertinent information be provided to the subjects later, if it's appropriate, how one is addressing that issue really determines, or is part of determining whether or not you're in a minimal risk situation.

PROF. CHARO: No, actually, no. That's actually from the regulatory language. It's one of the criteria, and that's different from what I was talking about. This is --let's not get off on that now. That's actually a separate criterion in the regs about whether or not you can waive consent to begin with.

DR. MURRAY: I want to make sure to capture whatever... What do you want to say about minimal notion, minimal risk of genetics?

DR. GREIDER: I think you just summarized it a minute ago. That you have to incorporate the psychosocial harms --

PROF. CHARO: Certain forms of research raise the risk of psychosocial harm, which should be recognized as real. Certain forms of genetic research raise those harms. We should be cognizant of those harms where they might occur, and the only addition I have is that in our assessment of the overall risk level of a particular protocol, minimal or nonminimal, we should also be sure to include all of the steps that are being taken to prevent those psychosocial harms from occurring by virtue of information modulation.

PROF MURRAY: Because that last piece becomes a practical addendum to them. And I accept it wholeheartedly. I think it's right. Okay. We'll have that in the transcript of this, so maybe we could take this right out, put it in. This is one of the relatively uncontroversial parts of the report -- find some things to say about it, but I think we're there with that. The existing regs work.

We add some commentary about psychosocial harm. That's it? Okay. Next step. We have --at some point, we'll need to take a five-minute break for you to use the bathroom, stretch the legs.

DR. SHAPIRO: I think that's a request, as opposed to an observation. I declare a five-minute break. Yes, this is an announcement here.

MS. HYATT-KNORR: We have gotten taxis, and Dr. Shapiro, Dr. Childress, Dr. Scott-Jones, and Mr. Capron will be in the door-to-door car, which leaves exactly at 2:30 out front. Dumas, Brito, Greider, Cassell, Hook, and Speers will take --and anybody else we have forgotten, one or two more, if they are, can take the Americab Van, also at 2:30 out front. That's it.

DR. SHAPIRO: Okay. You have a five minute break.

DR. MURRAY: We have a little over an hour before people have to go to their taxis. If I could ask the Commissioners who are still here —. There is an issue that Harold and I are --would like us to spend some time talking about, that we have not really focused on. And it is important I think for us to decide whether we want to make this in the report or not. Should we ask for some process of community consultation or not? But we have an analysis of the notion of community in Alan Buchanan's X, which has been incorporated into this draft. We have Jack Killen's presentation to us about these responses in consultation in AIDS clinics, which may have some --certainly has some disanalogies that we'll review. Why don't we see if we can come to some closure about whether we wish to have community consultation of some form, albeit recommendation or not. The issue of community is on the floor. What do you want to say about it? Carol says yes. Is it, yes, you want to talk about it; or, yes, we could have it?

DR. GREIDER: Yes, I think that we should consider some sort of a recommendation that it be considered as a criterion when addressing issues of risk.

PROF. CHARO: I want to propose, possibly, a specific case to talk about, to help focus the discussion. In the newspaper last week there was an announcement that somebody had found an association between a particular marker and a 4-point difference on the IQS of already high IQ achieving people. They had done this research according to the New York Times article, specifically, only within the white population because they wanted to avoid the possibility of finding differences that stratified by ethnicity, national origin, or race, and used only white American citizens, as far as I know. I don't know if they used men and women, or only men, to avoid stratifying by gender. This is the kind of research I can imagine comes to an IRB, somebody is proposing to look for an association between test scores on IQ tests with all of the methodological problems we associate with IQ tests, and they plan to stratify by all of these high-impact categories, gender, race, ethnicity, class, language background, you name it, everything that has a social implication. Now, I would personally love to see a way for IRBs to incorporate into their thinking social justice issues, the way that I have been urging for years that they incorporate them in the context of not only who's included, like fertile women, but who's excluded, like -- I mean included, like sterile women, and who's excluded, like fertile women. Two major obstacles to the incorporation of these, and to this discussion. At least two major obstacles occurred, and I'd love to hear creative ways to get around

them. One is a kind of First Amendment-sounding issue, which is that there is the problem of a kind of institutional squelching of research that is too politically hot to do. This would be another avenue by which that research could be blocked. And sometimes that research is what we want to encourage; sometimes what I want to encourage is not what you want to encourage, and all of those usual problems. And the second is, assuming that that's not going to be an insurmountable problem, or it's a problem we're willing to live with, if they're going to engage in this discussion about social justice, what in the current construction of the IRB and the kind of professional credentials that these people have is going to prepare them for this discussion? And if they're expected to be seeking outside consultation, what, if anything, is provided by way of guidance as to how to go about getting that consultation in a way that doesn't either reaffirm bad opinions that exist there, where they just look for people to support existing views; or is inflammatory, or is inadvertently insulting, or any of the other number of problems we can imagine as we try to identify who the group is that is implicated and who the representatives of that group are. So kind of how to operationalize this, so that the cure is not worse than the disease.

DR. MURRAY: Just for reference, okay, I just want to point out that the section of the report which addresses this begins on page 142. It goes on for a few pages, if anybody wants to refresh themselves. Alex, you had a comment?

PROF. CAPRON: It seems to me that the group consultation issue arises in three contexts, one of which may be related to what Alta just said. I'm unclear how the example you begin with, Alta, leads to a group consultation model.

PROF. CHARO: If I would want to engage in this research, I wanted to do it stratified by race, gender, ethnicity, national origin.

PROF. CAPRON: Did you talk with 30 or 40 groups then?

PROF. CHARO: My point exactly is just --for those who want to see community concerns incorporated --social justice concerns incorporated -- into IRB review, how might one imagine reacting to this protocol proposal, in which I'm going to go out looking for a marker that is associated with a 4-point IQ difference, and I want it stratified by all these high impact groups. How would we want the IRB to react?

PROF. CAPRON: To me that is less an example of something for which group consultation is advisable. It raises a basic question of whether there is a genetic deterministic model which has certain implications for a social understanding and relationships. And you don't have to presuppose you're a member of any particular configuration of these many different groups that might come out of this to say I think it's going to be bad science. I think it's going to have pernicious impact. I wanted to suggest there are three different things that group consultation could do. One, consultation with a group, in order to design a study in a way which doesn't stumble on some aspect of the community, where you just don't know it well enough; or where the acceptability of the research to the community would be effected by the notion that you can --participation in the design. This often comes up, obviously, with international studies, where someone is coming in, who doesn't

know a culture well, and has collaborators from the culture provide that advice. The second is the use of the group as a surrogate, where you cannot contact practically the people whose samples you're using for the study, and you want to have some sense as to whether this type of research — looking at this question, with this population — would be acceptable to people who are likely to be in your tissue population. It is not. In other words, you don't know what tissues you're going to get. You've asked for tissues from some group and you go to that group and say are there problems with this that we ought to be aware of. It's related to the first, but it's distinct. The third is where you do have the ability to get individual consent and you use the group to say, "Should this research be done," because it's going to have implications about our group, which we don't want to have come out. Even if you could find 50 people in the group who say, "We're willing to participate." The latter seems to be highly problematic under the current regulations. Now, maybe when we get to *Belmont Revisited*, we'll decide that isn't as problematic. But the notion that some group could prevent the research on that ground that it's worried about the findings in a way that they can persuade you to design it differently, or to convey the results, in a more nuance fashion, or whatever. They just don't want the research done. But individuals say they do want it done. It's problematic. The other two uses strike me as desirable reasons for group consultation. Now, there --in any particular consultation the group could serve more than one purpose, but I would recommend that we draw a line and say that that third purpose is not something which should be required and imposed that the research cannot go forward, where the researcher thinks it should go forward, and make any appropriate phases of the design that, in a sense, individuals are willing to consent, or it's totally exempt from a consent problem. But the representatives of the group say we're opposed to having you do this type of research.

DR. SHAPIRO: Well, this is an area in which I understand the desire, on one hand, to reach out to groups because you think that -- one thinks that would improve the quality of the research, and that's all that's desirable, and so on; or that they might legitimate your interaction with the community, which would be desirable in an age of research. And I think researchers would be well-advised to do all of those things. I think it's just a good research strategy. On the other hand, when it comes down to regulations that we're going to write, we're not writing a thesis on how you should design research projects, or, and so on. And I'm very skeptical about --as you are. I thought from the latter part of identifying the group --and for a hundred -- I mean I have to give a long list of reasons why I'm very, very concerned about anything that asks for group consultation as part of the regulations, as opposed to whether you might want to advise the IRB, or someone else, to think about these things, interact with -- in some way. I mean I certainly would have no objection to that. The moral units here are very hard to identify, once again, beyond the individual. And the idea of --and I think quite seriously that no --or the comment that Alta made a few minutes ago, although I think --I don't know whether you meant it as a small matter or large matter. I couldn't tell. But this idea of giving some unidentified groups some power over whether you should do something or not do something, really worries me an awful lot. And so, I would not --I haven't heard any convincing arguments so far as why we should require it. Now, whether we want to advise and make some observation, I'm perfectly open on that issue.

DR. DUMAS: Well, I was on a concern that I had earlier, and that is whether certain types of studies or studies that are focused on specific populations might be considered unethical. And I would be hard pressed to define which studies or which populations. Although, if we think about some of the arguments, I'm drifting back to the 1960's. And if we think about some of the arguments that have been raised in the past, they could conceivably come up. And so, we would need to think very carefully about principles that would help people who are in the position of making the decision about a research project that might be --I don't think we're at a point of defining any study or any population as being prohibited at this point.

DR. MURRAY: Eric was next, Diane, and Alta. I'll let the Commissioners comment.

DR. SCOTT-JONES: I agree with what Rhetaugh just said, and I'm glad that Alex suggested that we have these documents with us at every meeting. The *Belmont Report* at the end of it has a very good discussion of selection of subjects, and the principle of justice. And I think that referring readers to this type of writing is sufficient.

DR. MURRAY: Diane, I just want to be sure I know what you're saying. So, you would not recommend additional community consultation?

DR. SCOTT-JONES: Well, I think I would do it very carefully, and I would do it in reference to widely agreed upon principles, such as the principle of justice in research.

DR. COX: I agree with what I heard both Rhetaugh and Diane just say. I think you could shine a light on this in terms of forming people --in terms of research design. My view has changed dramatically on this in the following way: I see if one is not careful, that it's very easy to justify a particular type of research by getting an identified person who "represents the group," and makes what you're doing okay. And I think that it's under this Part 3 that Alex was talking about, and the points that Harold made, that are really and very concerned. If we get into community consultation, where we let any one person speak for the group, it becomes a very political and cultural thing. I think with as great a potential for harm, even in my view, more potential for harm than good. So, I'm agreeing with what Rhetaugh and Diane said, and also with Harold said, which is to shine a light on this in the context of principles of justice and research design, but not formally change regulations in the context of community consultation.

DR. MURRAY: Okay. I have now Alta, Eric, and Carol.

PROF. CHARO: I think that the possibility of incorporating some concerns to the community in IRB reviews need not be limited to community consultations, and I think that's what we've all begun to focus on here. One could imagine, for example, an IRB that asks PIs or their IRB members to contemplate whether the research that's proposed has the potential to generate data that will be used — whether intentionally or unintentionally — by the PI, or be used by others, to stigmatize a group that's already having trouble in this world; whether that group is a social group that we're familiar with, like race and ethnicity, or it's kinship group, a particular family. That's a tool. It's not the same as community consultation. It's a tool that says we demand a certain amount of reflection. It doesn't implicate --it doesn't require that the reason we would prohibit it, if the

answer to these questions is yes, it could be like the national Environmental Protection Act; the kind of thing that just by virtue of asking the question and generating information, is supposed to then trigger in people a kind of inevitable series of reactions like, “Oh, I didn’t think about that, or oh, maybe I’m not happy about that, maybe I want to think about whether it’s worth doing. Is the scientific justification, social need to this research great enough that I want to pursue this by the PI?” More nerve-racking is the IRB saying is the social need for this great enough that we should risk this kind of political problem. It may point up hidden flaws in the scientific design of the study, because sometimes they are based upon underlying assumptions about what groups are relevant and which ones aren’t, that are not that justifiable when one looks more closely. But that’s a different set of tools for thinking about ways to incorporate community concerns. I don’t think we need to limit ourselves to community consultation. I think these tools still raise some of those problems I mentioned before, like the possibility of the IRB acting as a bit of a break on academic freedom. But, again, I’m amazed that I started out as being very nervous about community consultation, and, therefore, community, and now I find myself not wanting to get off of it too fast.

DR. MESLIN: It would be helpful to staff, since we want to take your comments and prepare the next draft, ensuring that we have covered all of them, that --that the point that Alta has raised is carefully considered. We, as staff, realize that there is an enormous literature, not only of the kind that Jack Killen presented to the Commission, on the role that communities can play in the design and involvement of research. But also, information that, for example, the CDC has presented and others, of both a conceptual and pragmatic nature, that covers the waterfront from consent of the community, to consultation, to engagement, to a variety of extremely important and distinct activities, where you both recognize that the community has a role, or may have something to contribute. And I would be --it would be helpful to us if you could give some further direction, if we were to present to you options or recommendations regarding the proper place of community, and I can suggest to you a couple of ways in which that might occur. The first way that could occur is in the first chapter, where amongst many of the issues that Kathi has identified, those concerns or things that have animated our discussion, it would be very easy to identify case examples in which community concern or issue have brought out increased attention to the use of samples, and it’s easy for us to do that. We can do it by talking about the BRCA-1 genes or the Tay-Sachs examples. These are not unusual cases. David presented them to us, and they are in the literature. They are in the media. And they’re in chapter 2. Secondly, we have a section here that’s buried in chapter 4, relating to informed consent, which may one day leave that chapter and go somewhere else. But it would seem I think to us, anyway, that advice on just what the emphasis, if any, that needs to be placed on community, you want us to present us to present to you. Because I have to say that there are a great many other groups who are moving in the direction of incorporating community issues, and not simply the ones that we presented here. We have an international chapter that we have not completed for you, and noted that in the staff memorandum. Europeans, Canadians, and others are addressing this. So, any advice you can give would be helpful to the staff.

DR. SHAPIRO: Well, I think I probably am repeating myself, and I apologize, since time is short. But for me it’s quite important that we distinguish all of those things that are important

in designing a research project. Things you would want to take into account, and all of the things you'd want to do to make your research as successful and as meaningful as possible, of which communities is one of a host of things that you'd want to consider in those research designs. Selecting topic — I mean, there are all kinds of issues. It doesn't seem to me that that is what this report is about in any way. And so, I would put those aside, not because they're not important, but because I don't think that's what we're focusing on here. And as regards other parts of community, where what role they might have in informed consent, in some sense, which might be directly relevant to some of the things here, I remain very skeptical, very skeptical. And while I certainly think that it wouldn't be inappropriate at the beginning, as either you or Kathi suggested, that you say that people are concerned about it. Well, it's true. People are concerned about that. That's one of things, but that's quite different from thinking that we need to address it in the context of the regulations that we're focusing on. And I am --Alta has raised the issue of social justice appropriately. But me, speaking only for myself now, I'm not prepared to give that role to any IRB, so that we had defined --not we, the Committee; but we, the society, had to find some other way to deal with that issue.

DR. MURRAY: The list I have right now is in this order, Carol, Steve, Christopher Hook, Diane, and myself. Diane, would you like to --is this urgent? Because I'd be happy to have you step to the head of the line, if you'd like.

DR. SCOTT-JONES: I'll wait my turn. I'll just make a little note of what I wanted to say.

DR. MURRAY: It would have been fine. If you want to speak now, go right ahead.

DR. SCOTT-JONES: Well, I'll go ahead and I'll make it brief. Because I think Carol said most of what I want to say. Like Carol, I'm glad that Alta brought this up. But I think if we try to deal with this issue in the context of this report, we won't do sufficient justice to the really serious problems that do exist regarding some groups who may not be treated fairly in research. I just want to remind our group that I attended a meeting of the French Bioethics Commission that was on racism in science. And if we were to really give justice to these ideas we would need to do what they did, and we would need to consider them more thoroughly. Because the issue isn't just that there may need to be consultation regarding consent — it runs through the whole research process. And, as Harold has pointed out, some of the issues are purely scientific, and not having to do with ethics. They are issues of what kinds of people are involved in research in decisionmaking capacities. I would prefer seeing the Commission deal with these issues in a deeper, more straightforward manner than giving just some passing nod to these notions in a way that we could do in this report. I don't think we can do sufficient justice to the broader issues, having to do with both scientific concerns, as well as ethical concerns.

DR. GREIDER: I have two comments. And one is to respond in part to what Harold just said, in that, one can make comment on some community issues without saying it is going to be involved at the level of consultation. For instance, shining a light on the idea that the determination of risk is not just individual risk, but an IRB might consider group risks as part of a series of considerations that the IRB would consider when deciding on levels of risk. Without bringing

anything about having to consult the community, or bringing consultation into it. My second comment was more of a question, and this is directed at Tom. I understand what we're discussing here is what's going to become our chapter on recommendations. Is that part of what we're doing here?

DR. MURRAY: Yes.

DR. GREIDER: And when we talk about recommendations, it doesn't have to be recommendations of things we're going to change in the regulations, right? We are just going to have recommendations. And some of these could be not changing anything, but just highlighting that this should be highlighted.

DR. MURRAY: Right, we will have recommendations. And Eric provided a useful category station. We'll have recommendations, roughly, in potentially in four categories about consent: about the IRB process/procedure; about regulations which are changing rules; and about education. So, we could provide recommendations that IRBs be educated about certain things, or educate researchers. There are lots of possibilities.

DR. GREIDER: So, when I responded at the beginning that I thought community was important to include in the recommendations section, I did not necessarily mean that we had to change any regulations, or change the constitution of IRBs, but that we should do what we're doing now, is engage in where do we want to put the emphasis.

DR. MURRAY: Steve is the next speaker, and then Jim. I've got Jim on the list.

MR. HOLTZMAN: We're all in agreement with Diane's comment and Harold's, that there is a broad issue that's at stake here. The question is over six or nine months, community very much figured in the thought process of the subcommittee. And I've been sitting here trying to reconstruct why, and where it led us. It did come up in this constellation that issues pertaining to consent, or when there isn't consent, the fact that research findings could have implications for a community. Where we started in our thinking was having the IRB consider whether the nature of that research that was being proposed could have a harm to a community, if not --even if not to an individual. I think we were using the term, "could be stigmatizing." And that was sort of threshold question. And if yes, then engage in some process of community consultation. However, we then went to the next step and said, "Will that IRB necessarily know whether or not such a finding would be stigmatizing in the eyes of that community?" And so, we ended up with a position that said, "The IRB may not have that kind of knowledge, may not know." Therefore, it ought to simply ask the question, "Is it in the nature of this research that the findings implicate a community at all?" And, if so, then it should go to the community to ask them some form of consultation. I suppose, first off, to find out whether or not it would stigmatizing; and then, second, mark off whatever. So, the direction we're going here is, if I understood this notion of a light, and what we're asking of the IRB, is to ask the question, "Could there be a harm that could infect the community come under this research?" That's very different than where the subcommittee ended up. If I understood the drift, shining the light, it was, "Be sensitive to community issues, and that your research may have harms."

Okay. Are we comfortable with that? Because that's where we started the subcommittee, where we left that, because we said the group were asking that you should not assume they could know the answer to that question. Is that a reasonable reconstruction?

DR. MURRAY: I'm just having trouble following it. It maybe the hour of the day, or other things.

DR. HOOK: Thank you. I'm sitting here as an IRB member, and I'm trying to figure out how this would play out --you know, how we would respond to a similar situation. We actually have been working very hard to be more inclusive in our making sure that there isn't language discrimination, and some of the protocols come along, English, reading, and speaking to individuals to participate, trying to counter some of those types of requests, and this is just the opposite. And I guess what I would be concerned about is if we engaged in the community consultation, who, how many of the community, to what degree or majority is necessary to guide the IRB in its final deliberation. To be at the best place where we can intervene is trying to recognize that potential community risks, and presenting that to the individual, just as we talked about other psychosocial harms in our earlier discussion, and see if those individuals are still engaged based upon that information.

DR. MURRAY: Okay. And that list now reads me, Jim, and Alta. Let me indicate first that I agree with the comment Alex made toward the beginning of this part of the conversation about --individuals wish to participate in a research protocol, where they're being approached as individuals. It's difficult for me to say that they shouldn't be permitted to do that, because the group that believes they'd also be in that group doesn't want to do that. I can understand why a group might object, but I'm not sure that that objection -- I mean it doesn't have the moral power to say that you therefore may not participate in research. So, that's really one end of the spectrum. The tougher cases, the cases for which community consultation is a more sympathetic case could be made are places where, for example, you don't have to go to individual identified subjects. You've got samples out there, and you know the samples are identified as belonging in this group. And what do we do with those cases? Now, I began very sympathetic to the idea that we ought to try to make a model of community consultation work. I would still be happy if I thought we could do that. I'd like to see us do it, if it were possible. I have become increasingly skeptical to do that in a way that was defensible and practicable. And, quite frankly, I have found the arguments -- the problems identified by Alan Buchanan's paper, well stated and quite difficult. Just to remind you what they are, they begin on 145. It's the problem of identifying the relevant community, because all of us are members -- of overlapping communities. It's not always an overwhelming problem. If it was second generation Italian-Americans, I know a part of that community. The fact that I'm also a part of other communities is irrelevant. If this is the issue, if that's the community here, then it's easy to tell who's a member and who's not, relatively. A second problem is that the consultation can become coercive; that is, once a community or leaders in the community are mobilized, they may pressure people to participate. A third is --this is, I think, one of the most persuasive. He says, "It's a profound mistake to think that either a community's values, or who speaks for those values, can be readily identified." The more we know about any group, the more we tend to see diversity within it. There's a couple

of more things, questions about, contexts about what the community's authentic values are, and the fact that people we consult to the extent that they represent any subset of the community, may be advancing the values of that subset rather than that of the community more broadly understood. Those are pretty tough problems to overcome. And we have representative democracies, which make a somewhat successful effort to do some of those things. We're not going to ask for anything nearly that elaborate or extensive. But I'm not sure that we can come up with a good method of community consultation, a good model, that can respond to these sorts of problems. I say that with a lot of regret, but maybe somebody can help me on this. Jim and Alta are next.

DR. CHILDRESS: I think I agree that on the basis at least of what I've heard, that probably we can't in this report come up with the kind of model that we could argue very strongly for in terms of regulation just to reiterate Harold's point earlier. That we might be able to offer some advice, at least about the importance of considering community consultation particularly, in terms of concerns about harm and concerns about injustice. Two other points to make. One is that if we revisit *Belmont* at some point, then one of the major concerns that would be relevant there would be looking more closely at community. A point that goes all the way back to our very first meeting where Zeke Emanuel said what we need to do is look at the principles involved and now add a principle of community. So this is something that perhaps could be flagged in this particular report and then placed on attention to it over time. And I will also note that the Human Subjects Subcommittee—when it existed as a subcommittee—with the authorization of the full NBAC did make a contract for a paper by Charles Weijer on community. That paper was submitted in draft form. Eric and I made a strong, we made some suggestions for revision. And it's just been resubmitted in revised form. And will be available, I guess, shortly, Eric? And then I think we had a paper earlier from Bill Freeman on community consultation; in particular, in relation to the Indian Health Service. And that's another one that we might want to keep in mind as we're thinking further about these issues.

PROF. CHARO: I'd like to make three points. First, with regard to prospective collections, that is, collections that take place after the time that our recommendations are made, and in a ideal world, the recommendations are brilliant and everybody pays attention, there is a possible out for some of these things. And, in fact, the Wisconsin documents that were distributed give you an example of it. In which people who are being solicited for research, whether or not their tissues are going to be used in an identifiable or linked fashion, are told that there's every possibility that it'll be used for research that they might not approve of or that might stigmatize a group that they care about whether or not they're a member. And that they should keep this in mind before saying yes. But that we can't predict it all, and if you're worried about this in the slightest you probably should bow out. So there is some degree of "out" that can be identified for prospective collections.

The problem is really with the existing collections, where people didn't contemplate this at the time. And I'd like to remind people of one of the areas in which this has arisen to kind of bring us back to the costs on both sides. Because I think we're understanding well the costs of one particular form of community involvement, the consultations as you've outlined them, Tom. But a lot of this lately has come to the attention of the newspapers, is in the context of Ashkenazi Jews,

who had a fair number of tissues that had been collected in the context of Tay-Sachs screening. And the researcher who had that collection found that it was a convenient collection to use upon some very small motivation when he began looking for genes that had to do with other diseases, specifically cancers. And although I'm a member of this group, and our overlapping identifications, and although I therefore share in whatever stigmatization there is, I don't personally feel stigmatized. I don't feel like I now walk around as an Ashkenazi Jewish woman labeled "cancer risk." I think smoking has already done that; maybe that's why I'm insensitive to the ethnic slur. But I do appreciate the fact that some people do worry about this. And I'd like us to keep the historical context in mind. Because this happens over and over. We've had public health programs that have given people the notion that only immigrants get certain kinds of diseases. And so immigrants are viewed as dirty and contagious. And they're the ones who have malaria and cholera and pneumonia and tuberculosis. We've seen in more recent the years the political effects of diseases that are investigated only with reference to certain groups. When HIV, then HTLV, was being investigated only with regard to gay men, and was still called gay-related immunodeficiency disorder, the political implications of support for research, reactions in the public health stage to prevention and treatment, were wildly different than they were when we began expanding that research into all the communities, beyond gay men, beyond drug addicts, into the "innocent" hemophiliacs, and then the general population. So that, there are truly, there are significant costs to not recognizing in some way the degree to which our choice about what we study, how we study it, how we stratify it, and how we characterize it, can in fact have direct and indirect effects both on our medical priorities, and on our kind of social attitudes. And that's why I, without having the particular ideas in mind, would still welcome ideas other than community consultation with implications for enrollment, which I think everybody here has pretty much dismissed as a realistic notion. Encourage anything creative. I know the staff has given us some things about what's going on in other countries, and I confess I now couldn't find them if I tried for a thousand years. If there is a way to collect some of that material again, I would appreciate it because I think it would be wonderful to see if it's possible. It may not be possible to find some way to incorporate this discussion in a way that is not oppressive. I'm not advocating a return to the Soviet style of "this research is too dangerous to do" attitude toward the scientific establishment, which is the end of the slippery slope. But I do think that there are speed bumps on that slope.

Finally, and last, and I'll close, I do think that it's important to not continue to think about community only in terms of big social and political groups. Kin groups are also community. It's a much narrower problem, they're much more identifiable, they are identifiable as the relevant group. Also, they are somewhat more identifiable, almost to the point of becoming human subjects themselves, but not always, by virtue of the examination of the index subject. So that we may want to think in a discreetly different fashion about pedigree studies and kindred studies. And maybe not call that community, call it something else. But make sure we don't lose that in the mix. Because that's very much implicated by the tissue research.

DR. MURRAY: On the list are Diane, Larry, Carol, Alex. Diane?

DR. SCOTT-JONES: I'll try to be brief, because basically I'm going to be repeating what I said earlier. I agree with what Alta has just said so very beautifully about historical injustice.

And I also agree that we should consider issues that arise from kinship separately from the idea of community. I think that's very, very different. But I think the answer to the questions that Alta has raised about historical injustice has to be handled very differently from what we can consider here. And maybe the Commission might want to consider those issues at another time in another report. I would be very glad if the Commission would. The problems arise because researchers are themselves a community of sorts. And researchers belong to the various communities that we're concerned about. And problems arise because researchers in our society are mainly from one community and not broadly taken from all the communities that are affected by research. So, the answers to the problem can't be resolved by community consultation or by anything that we can consider in the context of this report. They run much deeper, and they have to do with the nature of science, who's a part of the scientific enterprise and who's not a part of that enterprise. And it's those issues that we would have to address if we really were going to resolve the issues of social justice or injustice that Alta raised.

DR. MIKE: In our past discussions I thought we had dealt with this issue and laid it aside. And what I mean by that is as follows; I don't think we ever seriously considered getting community consent for any of these, in any of these areas. I think the part that was most persuasive from our operational standpoint was that, especially, I guess, in AIDS research, just a process of involving whomever you call community in the design of the research protocol itself was found to be useful. And I agree with Harold that from our standpoint that's more or less a tangential issue for us to consider. So I would consider this as two analogies. One is that there's a lot of fruit on the tree but a lot of them dropped off before they're mature and they die as issues. Others, you've got to wait till they're ripe to pick. And they're not ripe yet. And the other one is that when we wring our hands a lot, we wring our hands and then go on.

DR. MURRAY: Carol?

DR. GREIDER: Again, I just wanted to say that we don't have to bring up all of the issues of community relative to consent or consultation. And I'm going to bring up these tired old 50 samples again that we were talking about earlier. We have 50 samples that are sitting in a repository. You don't know who they are or where they came from, but you get some information about them that they just happened to all have been tested for Tay-Sachs. And now you go and do some study on those 50 samples, and you find a finding. Well, that implicates a community, although it doesn't implicate any one of the people in that community. Should we maybe flag for IRBs that there is an issue that one should consider besides individual risks?

PROF. CAPRON: I want to respond to something that Diane said in her previous comment, and pick up on Carol's and Steve's, I think. If we are, as far as I can tell, now in vigorous agreement basically, that the one side where an individual wants to participate, the group can't override that, and we had difficulty even knowing what the group would be there. And on the other side, agreeing that while we don't want to spend a lot of time on it, Larry, it's worthwhile noting the value for investigators of an IRBs of having community consultation to improve the design and acceptability. I think there is still this intermediate category, where we're talking about not having

consent of the individuals. After all, that is a huge thrust of the report that we're talking about. And here, Diane, I don't think we can put this off for a future report. The full consideration of community and all its implications, yes. That we're not going to get to in good detail here. I totally agree with you. But if the question is, if you're using Tay-Sachs samples because you are looking in an Ashkenazi Jewish population, now looking for a new gene—which wasn't in anybody's mind at the time — the point that Steve made before, which I was glad to - I wasn't a part of your group, but I remember when it first came up - I think you were right in saying the reason for talking with the community was to get some real help from them understanding what they would regard as beyond the bounds, too stigmatizing, too risky. And this isn't like that first category, just good advice, this is a nice thing to do if you'd like to have a better research design. The question would be whether we would ever say to an IRB that where there isn't individual consent, and there is an identified population, an effort should be made to find reasonable representatives of that population and do a process which isn't exactly surrogate consent for the people you can't go to, these 50 people who 25 years ago gave their samples for Tay-Sachs. But rather is a requirement that you not approve of a protocol where the investigator hasn't made an effort to respond to the particular concerns of the community. And I would just push our discussion toward a recommendation. Put that on the floor as a motion, or as a, for the consensus, come to conclusions, if people don't like it, it shouldn't be in. If they do like it, we can move on from there. It seems to me it's different than the other two, it's intermediate between the other two. It's something stronger than just saying it would be a nice idea. It's part of what we keep calling the toolkit for IRBs. So that you not do what Alta just described, which is start a view that a particular population is problematic for one reason or another in a way which they would say, "Please redesign. This is a particular sensitivity, this relates to our particular vulnerability, whether we're patients with AIDS or any other group."

DR. MURRAY: Alex's suggestion is before us.

PROF. CHARO: Can you state - I want to be sure I got it - You're suggesting community consent?

PROF. CAPRON: I'm suggesting that as we look at this chart about situations in which the answer is you don't have to get individualized consent. Maybe - it's still regarded as a research protocol, we're beyond that discussion from this morning - but the question is do you have to get individualized consent? And you come to the point of saying well, it isn't really practical to get the consent here. Because the people are so dispersed who gave their samples 25 years ago. And then you get to the question, will waiving or altering informed consent adversely affect the subjects' rights and welfare? And this simply says we ought to recognize that if you have identified the group as the group that you're looking at as a group, part of that argument about well, you're a member of many overlapping groups is true, but it's only this characteristic that's being singled out by the researcher. And the subjects are not just these individual subjects. But someone who could speak on their behalf and say we, with this characteristic in mind, would be concerned about the stigma that would attach for whatever reason. And our advice to you, not required that we agree that you can do the research, but our advice to you would be the following. And the requirement would be the IRB would say to the researcher, have you made a good faith effort to do that, and incorporate the

findings of that process in your design?

PROF. CHARO: I'm sorry, but can I try to restate this really briefly so I understand what you're proposing?

DR. MURRAY: Well, do you mind, that you're next on the list. But it probably is useful to let this conversation work its way out.

PROF. CHARO: Do I understand correctly that what you're suggesting is the following: When an IRB is reviewing research that involves identifiable samples and it's asking can we waive consent, it has to answer four questions. And it answers, is it minimal risk? And in this case it says yes, it's minimal risk; is it practical to -

PROF. CAPRON: No, if it is more than minimal risk, it has to say...

PROF. CHARO: Oh, you would allow substituted consent for more than minimal risk research?

PROF. CAPRON: Not for identifiable samples. But we may be in a category — it depends partly, Alta, where we come out on the unlinked samples. Do you see what I'm saying?

PROF. CHARO: No. I'm sorry, I apologize.

DR. MURRAY: I'll give you a hypothetical. They're unidentified samples, but they have information about ethnicity, okay?

PROF. CAPRON: Except that at some point, the answer is going to be, if we resolve this morning's discussion by saying where they are unlinked, they are off the table, they are just off the table, they are not human subjects research. They are for the IRB, and everybody will have nothing to do with this, then we don't have any advice for the IRB because they're not going to be looking at the project.

DR. GREIDER: But there can still be community.

PROF. CAPRON: Yes. At the first level, that is to say, a good researcher will take some process of consulting with the community and involving them because it'll improve the research and so forth. You see, the problem, Carol, is there wouldn't be any process if there isn't a project that's undergoing review. So I'm assuming that perhaps if we adopt the second view of unlinked, which was going to say, unlinked is enough identifiable that it should have to go through some process. Okay? That's a possibility. It was one of the two options that I understood staff was going to develop. Then the IRB looks at this and says, well, usually we require informed consent if it's more than minimal risk, and even if it's less than minimal risk. It is less than minimal risk. Is it practical to get consent from people? No, it's not. Is there any risk? Will waiving that consent adversely affect the subject's rights and welfare? And it's here that I will simply say they could take a broader view. And we could tell them they ought to consider taking a broader view of subjects than just these 50 people who they don't know how to contact anymore, and get somebody who is a stand-in for those people.

DR. MIKE: But it's somebody. It's still somebody, Alex, that I'm getting hung up on. Who is this somebody?

PROF. CAPRON: Well, in the case of the Tay-Sachs samples, the synagogue from whence they came, even if those 25 or 50 people from 25, 30 years ago, aren't even members any more.

PROF. CHARO: You don't know synagogue politics if you think there's one synagogue that could represent any Jew! You need at least two to represent yourself! Let alone the entire congregation.

PROF. CAPRON: In fact, when Hadassah raised these concerns, it had the meeting at NIH recently, there were other people from the American Jewish community, who were taking a different view. And I recognize that. But I think Steve is right. The sense of what counts as stigmatizing is going to be affected by the views of the group involved. And it would just be worthwhile knowing that the researcher had tried to take that into account. And if this doesn't - I mean, I'd like to see it shot down. If it's shot down, then it's off the table. But it's something.

DR. SCOTT-JONES: I think that Alex's recommendation would have the problems that have already been identified, and that is that you wouldn't know who to go to, to get that consent. And I think the first part of what you said is what I agree with wholeheartedly. And that is, you resolve these problems that we are suggesting might be resolved by community consent at an earlier stage in the research process. And that is by having contact with relevant members of the community prior to the design of the study, as you're understanding what the nature of the problem really is.

PROF. CAPRON: That's the thing which I have in mind. The question is whether we say to the IRB, when you aren't getting consent from the individuals, is there a higher expectation that will happen? Or is that just sort of a nice little bit of advice? And I'm saying, a higher expectation.

DR. SCOTT-JONES: Okay, that part I agree with. I thought you were then going on to say that you would in lieu of individual consent get consent of someone representing community.

PROF. CAPRON: I was saying in situations where the IRB, where the researcher came to them and said "I don't want to get individual consent," and the IRB said "Yes, we agree, you don't have to, because it's not really practical to do so." It's in that kind of process that you just described as saying, that the researcher would say, "But I did go out. And when I was designing this, I focus-grouped it with the following groups that have the relevant characteristic that I'm looking at. And they told me this, and I redesigned it this way." And rather than that just being, well, that's a nice thing to do, we expect to see that you made some effort in that regard. Because we don't have any way of getting direct consent. And frankly, I would think in some of these situations, if Temple Beth-Israel in Baltimore was the source of those Tay-Sachs samples in 1970, you can go back to that temple.

DR. MIIKE: But, Alex, suppose they did do that, and the researchers come to the IRB and they say, “You know, we went out there and they are absolutely opposed to this research, but it’s a good research design nevertheless.” Is the IRB then going to say no research? Then that’s a veto power.

PROF. CAPRON: Why would they oppose the IRB I would say?

DR. MIIKE: I don’t care. I’m just saying that suppose that the end result is whoever they consult with says no. So if you put the imprint on the IRB to support that, then you’re giving those veto power over a researcher. And you’re formalizing it in the IRB process.

PROF. CAPRON: I understand the problem. Suppose you knew that these subjects if you asked them would tell you don’t do the study. Just, I mean, my hypothesis. You could find those people, and you know if you found them they would say don’t do the study. Should the study be done, just because it’s “impractical” to contact them? And I’m saying that if you went out and you got a unanimous - I mean, Alta’s view is probably correct.

DR. MIIKE: No, but what I’m saying is you’re putting the best-case scenario. I’m just saying what if they say, after all of that, they say “no”?

DR. MURRAY: I don’t want to keep Bill Freeman waiting. Bill?

DR. FREEMAN: I’d like to present the Indian Health Service experience, both its applicability and I think limitations, which I did not include since I didn’t write it, in the paper that I sent you a long time ago. The problem is that sometimes a subject of research is the community. If you’re going to do research to find out what is the prevalence of the alcoholism gene in American Indians living on X reservation or not, the subject is the community, not just the individuals. So then the question is, well, if that’s the subject of the research, what are you going to do about it in terms of some sort of consent? Or, what I suggest is a better word and was the original word of the subcommittee, which was consultation. I guess, and I think, that one of the things that I’m about to say is that consultation I think is probably much more relevant. Community consent is not relevant.

DR. MURRAY: Right. We’ve given up consent months ago. We’re talking about consultation.

DR. FREEMAN: In the Indian Health Service, we do it because there is a tribal government, it does have legal authority over research. Those two things that are a model for some people, I think do not apply. But the problem that does apply is that one, sometimes the subject is the community and it is a subject or area that is a stigmatizing condition. There’s a second problem, and that also should keep in mind, which is sometimes it appears that the research is not stigmatizing. And yet it is going to be misused by people in society to stigmatize. If you keep in mind at least the issues and state them fairly, you can say although we can’t solve it or whatever, but I don’t think it would be appropriate for especially a lot of minority groups to not include those two facts. But the community is a subject, the research can directly stigmatize or it can be misused to stigmatize. And we’ve got plenty of history of that. That would be an appropriate way to at least begin to deal with it.

DR. MURRAY: Okay, we have some people in line. I'm going to ask Eric. Eric had a small thing he wants to give us.

DR. MESLIN: I just want to know whether you wanted us, in working up these recommendations, to acknowledge what the FDA already includes under its existing regs? We talk about it on page 18, which refer to FDA's ability to ask for IRBs under FDA's jurisdiction to engage the community in a consultative mode. Do you want us to include that in any proposals that we send back to you?

PROF. CHARO: That was a diplomatic way of reminding us that there's something on page 18 we should have read.

DR. MURRAY: While you're looking at that, I've got David, Alta and Diane. Can we just remind everybody, people are going to be leaving for taxis in about ten minutes.

DR. COX: This will be very fast, and it's to emphasize something that Bill just said. Is that, right now, Alta made crystal clear to me at this meeting, is that the regs do not cover groups. Period. They cover individuals. So, a practical, pragmatic thing, in the human genome project right now, is that you have groups of individuals, their samples, that are groups; and that they're actually ethnic groups, although they're being called geographical groups. All right, I don't care what you call them, they're groups. And by the regs right now, is that those are situations that aren't going to be considered. Because if those are samples where you can't identify who the people are, those things are not being considered. Do we want those to be considered? I do. Now, how are they going to be considered? Well, I don't think that we can sit and say what the rules are. Whether you go back to the community, what you do. But I want the IRB to look at that research and see if the researchers that are talking about doing that have any thought to this at all. Are they considering the impact that this might have on a group? So I'm not looking for somebody to say, to trump it one way or another, but I want it to be considered. And that I don't know exactly how to instruct the IRB to do that, but I know if I was sitting on an IRB and I had a researcher coming in, and said, "What I want to do is I want to look for this alcoholism allele in this group of individuals that are anonymous except that they're all black." I'll tell you, and the researcher says, "But I'm not actually worried about it, and it's just science, man, I'm just going to publish the results." That wouldn't cut it with me. I mean, I don't know exactly what I'd ask the person to do, but that's not sufficient. So that if we don't do something, right now the regs don't cover this at all, and we have to do something, but it's not going out and finding the person to give us the answer. It's having some way of considering the problem.

DR. MURRAY: Alta's going to give us the solution in just one moment. But before that, those of us who purchased lunch through Henrietta owe her \$4.25 and I think she'd appreciate it if we'd give it to her before we got into our taxis. Alta?

PROF. CHARO: I can see two specific places in which something could be incorporated into guidance for the IRBs. One of them is not unrelated to Alex's suggestion, although I'm not in favor of his suggestion as I think it was formulated. Here are the two places I think it

could be incorporated. One, for people who are now being enrolled in studies, and who are giving consent, whether it's using existing tissue collections or new ones that are being drawn at the same time as they consent. It would be advisable, where the research protocol is designed in a way that it could serve to create a group ascription of some sort, to alert people to that in the consenting process so that they have a chance to make a reasoned decision about whether or not to participate in this kind of research. That is something that some IRBs do and others overlook, because they say that it's not medically relevant. But if it's relevant to the subject's decision, it's relevant. The second is in the use of existing tissues, where the IRB is contemplating a waiver of consent from the subjects. Now this specifically is in a situation in which it is minimal risk, and where it is already impractical to reach these people. There is this criterion that also has to be addressed by the IRB about how we can't affect the rights and welfare of the subject. It's a criterion that we've already identified, and this draft is one that is hard to decipher. And could be imbued with some meaning, and that could be one of our tasks as we continue on these things, and it's identified in the flow chart. One way to imbue that with meaning would be to say to the IRB "Look, certainly you want them to look and see whether or not this research affects their rights under State law, but you might also want to consult with obvious group affiliates, and say 'can you think of anything we've missed?'" It's a purely advisory thing. It has nothing to do with substituted consent or veto power. It's to help the IRB imagine what rights and welfare might be affected before they conclude that it is not affected, as part of their decision to waive the consent process.

DR. MURRAY: Alta, what about the cases where because it was fully unidentified, it would escape all IRB?

PROF. CHARO: I don't know, I haven't thought about that one yet. Has anybody else?

DR. GREIDER: Well, that would go to changing what is "human subjects?" Somehow David's case of doing completely anonymous research would have to become human subjects research, and go through an IRB.

DR. COX: This isn't the future. This is right now. This is happening right now.

DR. GREIDER: And at least have the IRB look at that kind of research. So the researcher has to be taught that if you do that kind of research, that does implicate a whole group, that's human subjects research.

PROF. CHARO: Well, the solution that people in the audience, as most people around the table were reaching, around the time we were taking the five minute break, was that where a researcher receives materials that are uncoded, from a repository that's keeping a list, so that the group membership is known, even though the one-to-one association cannot be made, that the researcher need not go to an IRB when he first gets the samples. Because that's still not going to be human subjects research. He does the research and suddenly says, "Oh, my. I've got a reason to want to contact all the members of the group." That is the moment at which the researcher and the repository need to be consulting with their IRBs. That's the point at which, if there's going to be a

contact made, it can be made in a way where the letter is being reviewed soberly. And that's also the moment at which, if there are any of these kind of group ascription community issues, they can be handled. Because you don't need to recontact for community issues.

DR. MURRAY: Thank you. We are simply out of time. I think there's some good progress on this issue. And I'm going to ask the staff and a few of us who've had the most to say about it, I would like to help to work with the staff to try to put some text before the Commissioners in the next draft. It may be alternatives, it may be that we think one is clearly superior. We will do that.

DR. MIIKE: Can we just dispense with this notion about a one-time consent through a Department of Human Services for all clinical tissues? There's a thing about consent there that I'd just like to just sort of drop off the table altogether.

DR. SHAPIRO: I haven't spoken to anyone else; I'm not in favor of rethinking that. Look, I want to thank everyone, and I know we ran short of time because of our discussions. I do want to remind you that you were all given a copy of an outline regarding one of our upcoming projects on the international research supported, conducted by the U.S. Please look over that carefully, respond to the staff, to Eric, or to Alex, or a sub. Whatever's convenient for you. We really would like your input on that because we're going to proceed ahead to try to plan that aspect of our work. You will be getting a report in the next proposal in the next few weeks regarding what we referred to as *Belmont Revisited*. A project which was our try to get in place for next spring to take this careful look, we and others, to take a careful look at the *Belmont Report*, and its principles and ask ourselves what the traditions, developments, how we feel about it 20 years later.

PROF. CHARO: We are going to finish all the current reports before we really get serious about the others, though, aren't we?

DR. SHAPIRO: Well, we're going to finish the current reports first, that's exactly right. This is somewhat going to be on a somewhat parallel track since it will involve a lot of people who are not on the Commission as well. So it's a little different kind of a project. And whether the Commission itself decides the issue on behalf of the Commission, its own views, is something we still have for discussion in another meeting. That would obviously come later. We do have to get our current reports out of the way. So that you should be receiving material very soon on those two things. I believe you have the international first outline already. And Eric reminds me you also have an outline regarding human subjects and our review of IRB's and so on. And please respond to us how you feel about that broad project as well. So that we will, I hope, at the Portland meeting, come very close to closure on the draft that we discussed this morning. By that time we'll have some feedback, public feedback on that. We hope we'll have this in a similar kind of situation by that time. And we'll just slowly start getting some of these reports out. So thank you all very much. I want to thank Tom especially for all of the help he has been in making the meeting here. Thank you.

DR. MURRAY: I just wanted to say that we hope to all come back and see Cleveland again. We all enjoyed having you here. And thanks for coming. Thanks to my staff who aren't in

the room, but I want it on the record, for putting in lots of hours on this.