44th MEETING

NATIONAL BIOETHICS ADVISORY COMMISSION

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I N D E X

P R O C E E D I N G S

PROFESSOR CHARO: Good morning. Since most of the commissioners are here, why don't I start first by welcoming the observers and asking if we can just take a poll of who is with us by phone. Anybody?

DR. McCURRY: Debbie McCurry is here.

PROFESSOR CHARO: Hi, good morning.

DR. McCURRY: Good morning.

DR. EISEMAN: And Elisa Eiseman is here.

PROFESSOR CHARO: Hi, Elisa.

DR. EISEMAN: Hi.

PROFESSOR CHARO: And is Alex Capron on the phone yet? Or Rhetaugh? Okay.

So we will probably be joined by two others a little bit later by telephone.

Marjorie has asked to take a few moments as we begin the meeting to talk about the time line for this report in light of the very substantial progress that we made yesterday on the recommendations for Chapters 2 and 3 so let me turn the mic over to Marjorie.

DISCUSSION: CHAPTERS 2 AND 3

MARJORIE SPEERS

DR. SPEERS: What I wanted to do is to share with you early in the meeting today before people start to leave what the time line would be for getting chapters to you again in time to review them at the December meeting.

Our next commission meeting is scheduled for December 7th and 8th. We would like to have a draft of the report available for you to have in your briefing books so that you have ample time to review them before the December meeting.

This means that we, the staff, have to have the materials ready to go by November 22nd. That is essentially a month from now. So what we are proposing as a way of operating would be we will take the suggestions that you have given us yesterday and today, we will take those suggestions and begin to revise the report.

We will over e-mail send to you those revisions and I am suggesting that we send them to you in pieces so that, for example, we will send you the text and recommendation for the definition of research. You can look at that. We will send you the piece on the risk analysis, the text and the recommendations for you to look at. We will redo all of the recommendations and send that to you by pieces so you can comment over e-mail.

If you comment fairly quickly over e-mail then we can make another set of revisions and then include all of those in the chapters that will go into the briefing book. So part of the reason I am telling you that is that we essentially have about a month which in some ways sounds like a lot of time but it is not and we need you to respond quickly when we send things out to you.

Also, we had gotten e-mails from Bernie and Trish with their comments on chapters 2 and 3. If any of you have

additional comments please e-mail them to us, if you can, in the next couple of days so that we can incorporate those kinds of comments into the revised drafts.

PROFESSOR CHARO: Okay. Bernie?

DR. LO: Marjorie, could I ask you to play out the rest of the time line and jump ahead to when we plan on publishing this and do we plan on trying to elicit public comments and what the time table for that would be?

DR. SPEERS: One scenario would be that you look at the full report in December and based on what you see in December you feel it is ready to go into public comment after the December meeting. We would assume that you want perhaps a few changes to the December draft and so we would make those changes using a procedure similar to what you used on international where we make the changes, we share drafts, but we essentially try to get a draft of the report out for public comment by the end of December. You know, 10 to 15 days after the meeting, recognizing that the end of December falls into holidays so we would want to get it out before the holidays.

It would then be in a comment period for some period of time. Generally we have used 45 day comment periods. That is what we are using for the international report. But because this is going out right before the holidays we may want to extend that 10 or 15 days to allow for the holiday period. That would then put us into mid-February.

We would then need to analyze the comments and report back to you on those comments. That is somewhat based on the

number of comments we get as to how long that would take but, you know, we should be able to come back to you then in March or April with a final report for your review and approval.

Do you want to amend that at all?

DR. LO: I just wonder if we should have a plan B for trying to issue something by January.

DR. MESLIN: Bernie, among the other scenarios, we are very mindful of the administration that asked us to prepare this report will no longer be in office using the time line that Marjorie has just described. So among the other scenarios that we have worked out is following the December meeting if there has been agreement about the principle recommendations, if not every single line of text, then that material in executive summary format could be forwarded immediately to the NSTC and made available with the caveats that this is for public comment.

It is not as drastic a situation given that all of our recommendations will have been vetted publicly anyway. There will not be dramatic surprises. I think the way this report has evolved is there has been a tremendous amount of outreach, perhaps more than any other report, that has been prepared in terms of going to federal agencies, informing IRBs and the like. So that second scenario is a -- I do not want to call it a fast track scenario but one that is anticipating being able to produce a document fairly quickly for the White House.

DR. LO: I mean, another potential way to think about this is to try and identify issues where we really do have

consensus or agreement and start with those and then on other issues where we may not be able to think them out as fully or to reach agreement, we may want to shift back into a position of saying these are issues we have identified that need further discussion. But I would strongly favor trying to have a scenario in place where by the December meeting we are able to issue something that we stand behind and would make a contribution.

I think a lot of what we have done over the last day or so we are agreed on and there are other things which are much more difficult, and if we can sort of try to identify what we do agree on that might be helpful.

PROFESSOR CHARO: Bernie, I would just point out that we do have a meeting in January that takes place before the inauguration so there is a meeting in January that takes place before the change of administration, which offers a second opportunity to issue a consensus statement on key areas.

Larry?

DR. MIIKE: Based on yesterday and assuming we do not backtrack too much, I think we can -- I feel pretty confident we can issue a consensus statement soon after the December meeting. We may get hung up in some of these little details but the big topics we have already covered and basically agreed on.

PROFESSOR CHARO: And, indeed, if I may, the game plan for today involves going through Chapter 4 to make sure we get there and then going back to some key issues in Chapter 2 and 3

around which there was not yet complete consensus or full enough discussion yesterday. In most cases there was a great deal of consensus about the sentiment behind recommendations but not necessarily around the specific wording, and we will not attempt to redraft today but there were a few items where we thought it would be good to go back and get better feedback from members so that the staff can accurately portray people's preferences.

Eric?

DR. CASSELL: Well, I am getting it out, I -- this proposes a really complete change of an existing system and I think it ought to go out as it -- when it is ready. The administration -- I mean, I cannot conceive of there being difficulty about this aspect of our work since there is a need for it and so forth. If it goes out without the substantiating reasoning and all that with it then we stand a chance of it not coming into being, not having the impact that we want it to.

DISCUSSION: Chapter 4

PROFESSOR CHARO: Certainly if we continue to function on a regular basis as a commission the work will continue and the substantiation will be developed.

Okay. All right.

With that, why don't we turn to the recommendations for Chapter 4. I hope everybody had a chance to look at it. It came after the main package. And for those who somehow did not get it delivered to their homes or offices, a fresh copy was delivered yesterday. Obviously it has an interplay with

Chapter 2 so some of those issues may come back to circle around to us.

Bernie?

DR. LO: In the spirit of trying to prioritize the 16 recommendations here, and it seems to me there are some that seem more important than others, I would suggest rather than taking them in order we -- the issues of single IRB review of multi-site studies and certification seem to be the core issues an I think some of these other things -- I am all for improving college, grade school and high school education but let's put those off until later.

PROFESSOR CHARO: Is that okay?

DR. SPEERS: It is okay with me.

DR. CASSELL: On the other hand it is not controversial.

PROFESSOR CHARO: All right. Why don't we -- the -- why don't we do what Bernie has suggested because everybody seems to fairly feisty this morning and we will turn then directly to Recommendation 4.9. Right, is that the one, Bernie? And then we will return to the others in order.

Tom?

DR. MURRAY: That move surprised me. There are a couple of other issues that I think are equally important, and I hope get raised. One has to do with the composition of IRBs.

PROFESSOR CHARO: We will absolutely get to them. It is not as if we are not going to get them to all but if you

would like to get to this one first so it gets the fullest discussion, and then we will move on to everything else.

DR. MURRAY: Okay.

DR. MIIKE: Can I suggest a different way then? Can we just sort of start off with one and see if we want to just sort of skip it; two, if we want to skip it; three, if we want to go on --

PROFESSOR CHARO: Why don't we just stick to 4.9 and just get started? It probably will not matter in the end as long as we get through all of them.

DR. MIIKE: Not the way that I understand we work. We are not going to get through this list.

PROFESSOR CHARO: 4.9. What did people put in their coffee this morning?

Bernie, did you want to start since this seemed to be of such concern to you?

PROFESSOR BACKLAR: It is the salt.

DR. CASSELL: We are on page 49 of 2E.

PROFESSOR CHARO: Bernie?

DR. LO: You know, I think I support the idea that a lot of -- having ten gizillion cooperating institutions when you do a protocol probably, you know, is not worth the effort.

Another thing -- I have concerns about two things. First, there is not a good model of how this works. Britain has tried something like this and their first published results in their first year or so of experience is there is a horrible

-- at least a transition period and a real concern whether it will work in practice.

The NIH has a couple of -- I do not want to say experimental but they are trying to see if they can develop a central IRB review mechanism for some of the cooperative cancer trials and ECOG has a similar type of effort. I am just concerned that we need to separate out the idea of trying to cut out redundant review while (a) being mindful of IRBs feelings that they need to sort of have their hands in the pot for a whole lot of reasons; and (b) it is not really clear how this is going to work.

So some of it is tone and sort of making it more sort of we have to figure out a way to do this rather than we have got to permit IRBs to sort of, you know, defer to a central institution. And some of the other language, which is more minor is that concerns in a real multi-site trial, how is the central IRB going to know about the particular needs at each of the institutions?

And what we hear from IRBs when we ask them why is it important for each of you to review this multi-site protocol, they say, "Well, we kind of know our subject population and what really goes on here, and we are afraid a central IRB will not know that." So we have to figure -- you know, at least in the text. And then there is a concern of we kind of know who the crummy investigators are that we have to kind of pay more attention to and a central IRB may not know that.

So I am just saying that it is again a problem of the recommendation versus the supporting text and sort of the tone of the recommendation but those are some of the issues that I want to sort of pay some attention to as we work through 4.9.

PROFESSOR CHARO: Further comments? Larry?

DR. MIIKE: I do not know or have any experience with IRBs but listening to what Bernie says, it seems to me it is not incompatible with a designated IRB primary with issues around investigators and local populations, it is still left to the flexibility of the local IRB.

PROFESSOR CHARO: Trish, did you want to add something?

PROFESSOR BACKLAR: I actually agree with what Larry said.

PROFESSOR CHARO: Eric?

DR. CASSELL: Well, I also think -- I think the idea is a very good one and I do not think it takes autonomy away from local IRBs. Mechanisms will be worked out relatively quickly for local IRBs to have their say because they will anyway. But the central one cuts down on the amount of work that is done.

PROFESSOR CHARO: Tom?

DR. MURRAY: The language of our recommendation as currently written could be read to suggest that we know the answer. Namely that this is exactly the shape this change should take. I think everybody recognizes the problem, which is on the one hand very arduous and in some cases inconsistent

when used by multiple IRBs. I do not think that is desirable. I think few people think that is desirable. On the one hand, the whole IRB system history has been to sort of recognize the local decision making.

I wonder if we could simply rephrase it slightly by saying that the appropriate agency, whatever phrase you are going to use there, should develop -- I do not have the language -- but basically should, you know -- the instruction should be for them to pursue this goal to develop an appropriate method of minimizing multiple IRB review of so and so and then should issue regulations to implement the solution thus developed. That would be a little less presumptuous on our part. It would give them a little flexibility. I mean, some would regard that as a stepping back from the position and I would understand but I think that might actually be more desirable.

PROFESSOR CHARO: If I may pose a question for people. The way the recommendation now reads, as Tom said, is rather strong and it could be understood to suggest that under no circumstances ought multiple IRB reviews be permitted any longer. A second way of presenting this would be simply to say let's remove all the obstacles that currently exist in multiple IRB reviews. We can encourage single IRB review but where local IRBs want to continue exercising their own discretion they continue to be permitted to do so.

Now in the text it identifies structural reasons why IRBs may find themselves anxious to exercise independent

review. For example, concerns about legal liability might lead their risk managers and general counsel offices to encourage them to retain some local control.

Is there a strong sentiment on the table about trying to stop local IRBs from continuing to do second and third reviews or is the sentiment rather to simply remove obstacles to single centralized review but not try to force it on the system? Just for the sake of clarity here around the table it would be helpful to know which it is that people are more supportive of and why.

DR. CHILDRESS: The second.

PROFESSOR CHARO: The second.

DR. MIIKE: But what is the substantial difference between those two positions? I mean, isn't it the multiple IRB that is the obstacle, that is the redundancy? Everything I have heard in testimony is that is the issue.

PROFESSOR CHARO: I am sorry.

DR. MIIKE: I mean, one is to -- what I am saying is that -- are we going to rephrase it in a nice way when there is no difference between obstacles and multiple reviews by multiple IRBs? I do not understand the substantive difference by rephrasing it the way that you suggested.

PROFESSOR CHARO: In terms of the way the regulations are now written?

DR. MIIKE: No. In terms of our recommendation. I mean, it is nice to say we would like to decrease obstacles, et

cetera, et cetera, but isn't that the main point here that it is the multiple IRB review and the redundancy that is at issue?

PROFESSOR CHARO: I guess, I am just not quite following the question. Why don't I wait for Jim to speak.

DR. CHILDRESS: Well, it is the requirement for the multiple IRB reporting. I mean, that is at issue, right?

DR. MIIKE: Right.

DR. CHILDRESS: And so here we are moving the obstacles to allow it to occur rather than rushing -- as -- requiring that only one IRB must review and approve a study, and maybe that is what it would amount to in removing the obstacle. Maybe we do end up with a just slightly different take on the same.

PROFESSOR CHARO: Tom?

DR. MURRAY: I would like to hear what others have to say.

PROFESSOR CHARO: Diane?

DR. SCOTT-JONES: I was wondering if we could accomplish what Tom was suggesting by reversing the order of 4.10 and 4.9. 4.10 recommends the testing of various models from multi-site study review and if that is presented first, and then our recommendation would seem softer than it does now if it came second.

PROFESSOR CHARO: Bernie and then Bette?

DR. LO: Let me defer to Bette since she has not spoken.

MS. KRAMER: Oh, that is all right. I wonder -- the recommendation appears not complete to me because where, for instance, within 4.9 where would adverse reports go? Would they go to the central IRB? Would there also -- would the local IRB have the option to continue to collect their adverse reports? It seems to me that the recommendation does not pick up on all of the language that precedes it in terms of its very full discussion of the problems.

PROFESSOR CHARO: And, of course, some of those issues about adverse event reporting will be picked up in recommendations 4.7 and 4.8, which talk about the role of the central office and of the sponsors and ensuring that adverse events are reported and then provided --

MS. KRAMER: Yes. Well, my concern is just that if we are going to recommend the use of a central IRB that we flesh it out.

PROFESSOR CHARO: And that would include incorporating some of the specifics on the way adverse event reporting would be handled. Other comments?

MS. KRAMER: And I guess continuing review and every -- you know, all the requirements.

PROFESSOR CHARO: Bernie?

DR. LO: I actually like Diane's suggestion starting with 4.9 and to maybe strengthen 4.9 -- 4.10. I am sorry. Starting with 4.10 and strengthening it to say that the central office should identify and evaluate methods of avoiding duplicative review of protocols in multi-site trials or some

such language so not just other models but models that streamline and avoid what is felt to be duplication.

And then looking at 4.10, I guess the first sentence somehow bothers me. I guess some of these that only one IRB -- I am a little concerned about sort of finding the softest IRB to review something. The next sentence talks about a designated IRB and I like that a little better. I do not like this idea you send it out and the first one approves it and says, "Okay. Finished." It is like a grant, right. You send out five million copies and the first one that funds it you say, "Good, we will pull the others back."

And then in the third sentence I have a concern about knowledge of the participant population. I think there are populations and my concern is that in multi-site studies the population will vary tremendously -- may vary tremendously from site to site and the concern is they are -- the designated central IRBs got to know about the peculiarities of each site, which arguably the local IRB may have more intimate knowledge of. So just saying participant population may get over some of that.

PROFESSOR CHARO: Other comments? Question: Does it matter strongly -- does it matter a lot to people who designates the designated IRB? And, if it does, what, if anything, do we want to say about that? Keeping in mind that we not try to micromanage this but to identify those things we care about enough that we would want to create some parameters to this new exercise.

Bernie?

DR. LO: Again, I think this is -- it -- I mean, the general idea is a good one and all these details, the one Bette raised about what about the monitoring -- I think the most sensible thing for us to do is try and tie it in with the certification. I mean, I do not think every IRB should be certified to act as the central review IRB for multi-site studies. There probably should be an additional level -- it is like driving a bus rather than driving a car. It is an additional set of skills you need to have to be able to do that kind of work.

PROFESSOR CHARO: Trish?

PROFESSOR BACKLAR: And I agree with you, Bernie, because you may even want to develop different kinds of methods in which you would take a couple of members from each of the IRBs that are involved in the study sites and have a little nucleus, a little group that does this, some from each site and work on it instead of the entire IRB at each site doing it. So there are many different models that you might want to suggest and I think that that would be very much more fruitful because we really cannot make those decisions at this table. It is beyond our abilities to do that.

PROFESSOR CHARO: Diane?

DR. SCOTT-JONES: I really like Trish's idea of considering other possibilities and we already have that in 4.10 that we consider different ways of doing this and I think that there are various ways to handle the designated IRB if

that model is used. For example, in some multi-site studies one researcher at one institution is the lead researcher and it would make sense for that person in some cases to be the designated -- that person's institution to have the designated IRB so there are lots of ways of creative and probably equally good ways of doing this so I think it would be better to have some flexibility instead of making a strong commitment to a lot of very specific details.

PROFESSOR BACKLAR: Then it might be a very good idea for us to think through some of those possible models and put it in the text in some little box of variations of doing this because I could see as we start to talk about it we can build on these ideas together. We could do it through e-mail.

PROFESSOR CHARO: One last thing I just want to ask by way of just getting people to think and I do not have something in mind but since yesterday we continued to endorse the extension of the system to currently uncovered private sector research that is typically not affiliated with any kind of institution for which the whole notion of finding an IRB is going to be slightly alien. How do we go to independent IRBs? Is there anything in that universe that is going to complicate the question of the coordination of multi-center IRBs that people would like to bring up?

DR. MURRAY: That is a very good question, Alta.

I suppose the best hope there would be some sort of certification process and then accountability for IRBs --

PROFESSOR BACKLAR: I could not hear you, Tom.

DR. MURRAY: A certification process might be the best response to that with some accountability involved --

PROFESSOR BACKLAR: Yes.

DR. MURRAY: -- in obtaining certification. It is a very good question.

PROFESSOR CHARO: I saw a hand up.

MS. KRAMER: Me.

PROFESSOR CHARO: Bette?

MS. KRAMER: You know, I am wondering given the complexity of this and the fact that time is short in terms of our thinking it through and getting out a report if we ought to consider rewriting these recommendations along the lines of something like that we recommend that it move towards -- that the system move towards the use of a central IRB for multi-site trials and that there are -- that a model or that models be created and tested but specify what needs to be included.

In other words, that it is not only the prior review but it is the reporting of the adverse events. It is devising a system for monitoring compliance, et cetera, et cetera, et cetera. And leave it to some other body to work out the way in which it actually is to be done because that is going to be very tricky incorporating the private sector research as well. So we could -- maybe we would be serving a greater function if we specify what ought to be included and even possible roadblocks that needed to be considered.

PROFESSOR CHARO: You know, in order to make it possible to write something like that, it would be helpful to

make sure we all do have that kind of list of essential functions and so far what I have heard you specify are the ability to conduct the review competently, the ability to centrally gather and handle the adverse event reporting, and the continuing review process. Those are the things I have heard you say. The recommendation includes another thing that is listed as essential and that is knowledge of local populations. Would you rather continue to view that as --

MS. KRAMER: Well, and also to ask to ascertain that -- to ascertain that all the researchers, all the investigators who will be working on it have been properly certified, et cetera. I mean, I think if you go -- I think that the material that precedes the recommendation is very good and very, very complete and I think we can probably go through that and just glean from that what the requirements ought to be.

PROFESSOR CHARO: Okay. I just want to make sure that we do have that list so that it is easy to collate.

Bernie?

DR. LO: Yes. I just want to say it is sort of a points to consider type discussion that summarizes the text that goes before the recommendations.

PROFESSOR CHARO: Okay.

MS. KRAMER: It is a little bit like writing the rules and regs, isn't it? We do not have to do that.

PROFESSOR CHARO: Thank God.

Other comments, feedback before a second crack is taken by the staff at the --

DR. LO: Just one more thing to add to your list, Alta. The point, I think, that you raised earlier about how -- exploring how this would work in the private sector as opposed to a bunch of academic institutions.

PROFESSOR CHARO: I am not sure that it will make a difference. It occurred to me that is --

DR. LO: Well, I just think it is something --

PROFESSOR CHARO: Yes, it is a very different group of people and I had not really thought about what might be different.

Diane?

DR. SCOTT-JONES: I would just like to emphasize the suggestion that someone made earlier about the phrase "participant population" as if there is one population. I really like in the draft the fact that instead of naming vulnerable populations there is a very nice discussion of dimensions of people that might cause them to be vulnerable and I think it would be good if we could move away and just there say knowledge of expected participants or something like that and not suggest that there are necessarily discrete populations that will be targeted in the research.

PROFESSOR CHARO: Okay.

Anything else?

All right. The morning is young. If something comes to mind that people think would be helpful, please do not hesitate to suggest that we go back to 4.9 and 4.10 to add further detail to the guidance there.

Why don't we go back then to 4.1 and start taking things in order. And we will, as Tom mentioned, still come to some things that may be worth some fairly extended discussion.

4.1? Going once, going twice.

Bernie, Diane?

Bernie and Diane.

DR. LO: I have two kids in school so I have got school issues on my mind all the time. This seems like it is motherhood and apple pie but, believe me, the idea of a central office developing educational content standards is not apple pie to some people. That is the central government interfering with the rights of local communities, school boards, states, et cetera.

I mean, let's -- if this is meant to be an apple pie recommendation, let's take out the notion that the educational -- the central office will set standards. Is that what we mean? I mean, what exactly are we trying to do here because the idea of telling everybody what to do is pretty strong and that may be what we want here because we are -- you know, we think we are talking about telling every university that we work at what they have to do but if you just think about it -- how we would all feel being asked to implement educational standards formed by a central office in Washington, I think some of us would think, gee, I know how to do this better at my own institution. So I am a little concerned about the political implications.

PROFESSOR CHARO: Before I turn to the list, Marjorie had some clarification here.

DR. SPEERS: Let me just clarify what the sentiment was in case the words are incorrect. What we were envisioning in 4.1 was that the central office would outline the elements -- staying away from the word "standards" -- the elements of what should be in an educational program. That is what we are -- that is what I am trying to say here. Nothing -- nothing more than that. That local institutions can tailor the educational program the way that they want to in their institutions but the basic material of what should go into an educational program should come out of the central office.

In this recommendation I was not thinking about local school curricula. That we were addressing in 4.3. Because I understand all of the issues about how states and local school districts determine their curricula.

PROFESSOR CHARO: I have got Diane, Eric. I thought I saw another hand up on the side. Diane, Eric and Larry.

DR. SCOTT-JONES: Like Bernie, I agree with the general idea that education should be promoted but I guess I have a concern about the presentation of the central office earlier in the chapters as an agency that is somewhat remote from the every day research enterprise. And this, it seems, is making it somewhat closer by developing educational standards.

I also had a question about exactly what the phrase "education content standards" means. It used again in the subsequent recommendations and I was not sure what is meant by

education content standards or educational content standards. I would like some clarification of that. But I just have a question about whether this remote central office that is described as acting through its interactions with others really can have some impact on education content standards. Whatever those are.

PROFESSOR CHARO: Eric?

DR. CASSELL: Well, Marjorie, I think I -- also the standards has become a buzz word. What you said before is exactly what it is. Should develop the outline of the content that so and so should have. That is its job. This is what we think is necessary. How that is implemented is then a local -- becomes a local issue. If I were this office -- in this office I would probably say to Jim at the University of Virginia, "Would you people like a contract to help develop what you think should be an educational content," and so forth.

PROFESSOR CHARO: Larry, and then Bernie.

DR. MIIKE: Taking one, two, three and four together, I would rather see one as focused only on the research community itself because that is the expertise supposedly of whatever the central office is. And so if they are to -- whatever words we use, clearly they have -- they are the ones that can say what substantive content needs to be addressed in any kind of an educational development. I will not agree that we should extend this down to grade school level. I think we are just getting too narrowly focused here.

I mean, there is a whole lot of agendas on grade school level and to talk about research ethics to be taught in the curriculum of grade schools is a little ridiculous. I feel a little bit that way about the college curriculum but certainly not among students -- I can buy a little bit about the science curriculum where research ethics should be part of the science curriculum but I think it should be primarily focused on those very close or already engaged in research and that should be the focus of our educational objectives.

PROFESSOR CHARO: Bernie?

DR. LO: Let me just say having fought a lot of battles about what should be in the kindergarten curriculum, I have real concerns about getting dragged into this one.

(Laughter.)

DR. LO: Back to recommendation 4.1 because I agree with Larry the central focus here has got to be in the researchers. That is where the main problem is.

As I view the central office, what I think they could do best is to (a) put some money behind developing curriculum; (b) hold workshops; (3) hold consensus meetings, which seems to me very different than developing even the outline, let alone content standards.

I actually happen to think if someone were to go around and ask people who are actually trying to do this what do you think should be in it, you would get a lot more sort of from the ground up ideas than if you had a blue ribbon panel and even called the AAMC and AMA, and all the usual suspects.

So I guess I -- you know, as someone who has been trying to teach this stuff, I really would feel very unhappy with someone saying here is the outline for what you are supposed to teach. You just go off and do it. I do not have a lot of confidence that it will really be right unless we talk to the people who are, I think, now actually are honestly trying to grapple with this.

So I guess I would just say I am more of a believer in sort of turning to people who have the best hands on views and trying to start there and work on up as opposed to what it sounds like in 4.1, more of a top down approach.

PROFESSOR CHARO: Bill, and then Eric and Jim.

MR. OLDAKER: Excuse me. I think it is basically a nonstarter to try and mandate any educational institutions to teach anything. At the current time, there are no federal regulations that mandate any course be taught at any university or any secondary or primary school. So, I think, you know, if we try to swim up -- and there is a reason for that because there have been great controversies because people have different ideas of what should or should not be taught. Even the bilingual education act, which was once on the books, is no longer on the books. So I think, you know, it may be a laudatory goal but I think it would -- we would not get very far in the world out there trying to do this. Plus, I think, we would gain a lot of resistance from academic institutions if we said they had to teach a course since most academic institutions may choose to teach it. State colleges -- there

may be one state college in a state that may not wish to teach it at every institution.

PROFESSOR CHARO: I now have on my list Bill -- I am sorry. Eric, Jim, Tom, Arturo and Trish. Because I am also trying to keep track of time and make sure we get through everything, as you give your comments if you can also give staff an idea of what you would like to see instead, it will help at the end for them to know what to draft for the next round.

MR. OLDAKER: Can I follow up with mine instead?

PROFESSOR CHARO: Please. Follow-up with what you think it should be.

MR. OLDAKER: I think that the accreditation institution, whatever it is, should be actually separately certified by the central office, which will be probably either a state or a national level that deals with IRBs. And they should be empowered to develop a curriculum in conjunction with the separate office to teach courses. And then they should be encouraged to proliferate that throughout the teaching system. That basically is as it works in law and medicine currently through the various societies, and I think that is an -- people understand that kind of system and that probably would work and I think then they could be funded in various ways and people -- basically most courses like this are induced to be taught by funding and I think that is the other way to go about it.

PROFESSOR CHARO: Eric?

DR. CASSELL: Well, you know, we can see that this has just stepped into the middle of a political controversy about education in the United States. It is the same set of words and so forth and that is very potent getting in the way of what you want to do but I do not think we should leave the idea that education should extend down -- education about ethics should extend down to the grade school level. It does not have to -- content does not have to be laid out. Good reasons why it should will do the job and the suasive powers of whatever this office is, are usually sufficient. So it should say instead of content, the office should, by direction and by its persuasive powers, show how education in these matters should extend as far down in the educational system as is possible.

PROFESSOR CHARO: Jim?

DR. CHILDRESS: Building on what others have said, it seems to me that we may be moving toward making 4.2 the first one and whether we get agreement on some version of 4.4 as the second one is kind of ideal for colleges and universities, and then perhaps have a statement about the central office funding research into the best ways to teach research ethics or set up some kind of -- again, more on the funding side rather than on developing education content standards itself. If we did that we would have three recommendations that would fit together fairly well and I think with alterations in wording might be acceptable.

PROFESSOR CHARO: Tom?

DR. MURRAY: As I am hearing this discussion evolve, it seems to me that we should in the smartest course of action simply to drop 4.1 since it seems largely -- that content which is acceptable is largely redundant with 2, 3 and 4. That content which is susceptible to distortion and misunderstanding and discrediting of our larger recommendations is -- that is the -- what is original is easily susceptible to political distortion. Claims of central control, claims of, you know, ethical -- well, you can -- one can imagine if somebody is opposed to whatever we are proposing, there are lots of strategies they could take and I think 4.1 is leading -- at this point we are going to be leading with our chin so I would propose dropping one.

PROFESSOR CHARO: Arturo?

DR. BRITO: It seems to me that with all this educational -- when I think of education I think that the two main individuals, if you will, are the researcher/investigator and the participant. And one of the things that occurs to me is there room here for the central office to educate the general public. I understand the rationale behind education at the grade school, high school, college level and all that, but is there a role for the central office here to educate -- to have responsibility of educating the general public? I think there is a mention in here about journalists and all that. But maybe we take it a little bit further to put the responsibility on the central office to educate the general public who will be the participants, eventually, in the research given all the

obstacles that will be faced trying to implement this into the grade school or high school or even college level.

PROFESSOR CHARO: Bernie, Larry and then I think we may need to try to sum up and move on.

DR. LO: Let me make a suggestion for recasting 4.1. The central office should take steps to enhance the teaching of research ethics to investigators and IRBs. The central office may choose to do so through stimulating discussion and convening interested parties such as dot, dot, dot, the usual suspects. And funding the development of innovative teaching programs, research on effective teaching methods, evaluation programs and funding of workshops. Something to that effect. So give them more of a kind of stimulating, inspiring, or bringing people together role rather than telling people what they must do. I think that is an appropriate role for a central office to do.

DR. MURRAY: A point of clarification.

PROFESSOR CHARO: Tom and Diane.

DR. MURRAY: I want to know what Bernie is proposing because as I read 4.1 currently, it does not limit itself to investigators and IRB members. It covers the waterfront. So is it your intent then to narrow 4.1 to just that?

DR. LO: I would feel more comfortable doing that just because I think that is where the action is and that is where they should start.

PROFESSOR CHARO: Diane?

DR. SCOTT-JONES: I think that Arturo's suggestion of including some way to reach the general public is a good one. Bernie, would you think that could be included?

DR. LO: Yes, that is fine.

DR. SCOTT-JONES: I think that is good.

PROFESSOR CHARO: Larry?

DR. MIIKE: I agree with Jim's scheme if you all remember what he mentioned. Of course, the discussion has been going on for a while. I would agree with a variant of Bill Oldaker's. I do not think the -- whatever we call the central office should be the one that accredits but it certainly should be funding the kinds of groups that we have met with before that develop accreditation programs. And I think that is what we should just stick to, the accreditation side and not expand it because in this discussion we are talking about all the duties we are beginning to impose on the central office. I think the key here at the moment for the educational side is developing an educational program for IRB members and investigators and others directly related with the research.

PROFESSOR CHARO: If I can take a -- Bette?

MS. KRAMER: Well, one thing that might be added to that shopping list is to develop some kind of materials to be given to perspective participants in the projects so instead of embracing -- instead of trying to direct education for the whole public, at least speak to that narrow audience.

PROFESSOR CHARO: If I can try to sum up across 4.1 all the way up to 4.4 so we can try to make some progress,

would it be fair say what we are hearing is that there is agreement that the Federal Government has a role in encouraging education at all levels with a special emphasis on education in people who are most closely associated with doing research or being in research? That it should be looking for ways to facilitate that education - to delegation to other bodies as well as the preparation of model materials, et cetera, and guidance as to the content - that education at other levels of schooling would be desirable but certainly it is not the role of the Federal Government to dictate the content of the kindergarten curriculum in Oakland, and perhaps -- is there anything else essential that we need to give them by way of tone for the next draft?

Okay.

Why don't we move then to 4.5. Comments?

Bernie, Trish, Arturo? You always come in just as I am about to move on. What is this? Bernie, Trish and Arturo?

DR. LO: Let Trish and Arturo go first and I will go last.

PROFESSOR BACKLAR: No, no, Bernie. It is always nice to hear your voice.

DR. BRITO: Mine was very simple and straight forward.

PROFESSOR CHARO: Arturo will go first.

DR. BRITO: Given the discussion of 4.9 about allowing IRBs outside the institution or one IRB, you know, just the language here with institutions that can be globally monitored through the IRBs and what do you do if -- about monitoring

ongoing research, you just need to keep this in mind, this has to be consistent with 4.9. That is all.

PROFESSOR CHARO: Okay.

DR. BRITO: So the language of "their" as the pronoun.

PROFESSOR CHARO: Okay.

PROFESSOR BACKLAR: And actually mine is quite simple, too, and that is that none of this can happen unless we are sure there is money for it.

DR. CASSELL: Say that louder.

PROFESSOR BACKLAR: So that has to go in somewhere.

PROFESSOR CHARO: Okay. She said that nothing --

PROFESSOR BACKLAR: None of this can happen unless there is enough money for it.

PROFESSOR CHARO: -- none of this could happen unless there is enough money for it.

DR. CASSELL: Money. Oh, money.

PROFESSOR CHARO: Bernie?

DR. LO: This is a topic, I must say, I feel very confused about and I want to try and go back and start with the simple things. First, I think we should recommend that a better system of tracking and following up on complications from research studies need to be developed and we have to do better than the current fragmented system because I think we have to say that the problem has to be changed. I feel much more confident about that than about how to fix it.

I actually have concerns about IRBs doing this, whether they are the right group to do it, what their

relationship is to the FDA and the Data Safety Monitoring Board. Having much more experience on Data Safety Monitoring Boards than IRBs, I think in a big clinical trial, I actually think that is the place where adverse events can be looked at because they can be unblinded. They have the ability to gather more data to interact more with the data committee, the central data committee. They need to feed their findings back to the IRB, which they now do not do because of secrecy.

And similarly there is a parallel system with the FDA where you have got three people with responsibilities. I think we need to somehow say that the Federal Government, someone needs to sort out a way of making the FDA, Data Safety Monitoring Boards and local IRBs work together in a consistent system that serves the purpose of protecting participants from adverse events.

I would leave it open as to what role the IRB should play in this because I think it will depend on what kind of arrangements get worked out.

So, I mean, to the extent that that to me is one of the more serious things that the IRB needs to do in monitoring and follow-up. It is not really clear to me what precise role they should be playing so this also to some extent ties in with 4.16 and the role of the FDA and their monitoring as well but I just think that given that that is one of the key episodes that sparked the whole interest. The Jesse Gelsinger thing where people, if they report anything, were reporting to different people and do not talk to each other. We need to get back to

that level of outrage that how could people not know that serious adverse events are happening and not take steps to modify the protocol.

PROFESSOR CHARO: Tom?

DR. MURRAY: Yes. I thought we were talking about 4.5 but Bernie has jumped us down also to 4.7 and 4.8, and that is fine. That is -- if everybody agrees that everything is on the table.

PROFESSOR CHARO: They do kind of work as a collection, I suppose.

DR. MURRAY: Yes. Okay.

PROFESSOR CHARO: So feel free.

DR. MURRAY: Well, then let me begin with 4.5 and 4.6. There seems -- unless I a misreading these, there seems to be a certain overlap between five and six. Six is clear that this is -- this has to do with ongoing -- review of ongoing research which I have always thought the term "monitoring" applied. I assume that is what we are talking about.

Four and five both mention monitoring -- the same sort of monitoring in the sentence between on page -- on line seven. But then also talks about institutions developing mechanisms for monitoring their own IRB's compliance. That seems to me the novel element in four and five. So I would -- I would either bundle the two together, or if you think it worthwhile to keep them out, you can give institutions the central office perhaps -- I am using that phrase with long teeth here but the central office can issue regulations and guidance to define the

roles of institutions and monitors, and then tell us what those roles are. And then later -- and then, of course, six deals with the ways for IRBs about monitoring ongoing research. It seems to me there was a slopping over of the two.

PROFESSOR CHARO: Trish?

PROFESSOR BACKLAR: Well, I was going back to the text and looking in the text on page seven and seeing here where in lines 22 to 25 the three types of monitoring will be addressed here and then laying that out and somehow or other this does not seems as clear in these recommendations and I think it would be very helpful to go back and look at that and take the recommendations. One with each of these three types of monitoring and it would be much easier if you looked at the recommendation. You would know where you were.

PROFESSOR CHARO: Diane?

DR. SCOTT-JONES: I agree with what Trish just said. I also looked back in the text and I found on page 8 at the bottom another listing of what would be included, and there is continuing reviews of ongoing research, tracking changes to approved research protocols, tracking unanticipated problems with the research, and noncompliance in following federal regs, permitting direct observation of the research, particularly the informed consent.

So I would like to add to what Trish just said that there could be a better matching of these recommendations and the way they are broken down into these few recommendations to match what is in the text and to clarify how some of these ways

of monitoring could happen. Some of them are extremely difficult and some of them can be accomplished fairly easily but some, like tracking changes, tracking unanticipated problems, all of those would be very difficult to accomplish.

PROFESSOR CHARO: Eric would like to ask a question.

DR. MESLIN: Just as an organizing principle, is it more helpful to have recommendations focus on the function or on the group that is going to be implementing them because your list, Diane, which was a complement to Trish, would suggest that there would be recommendations relating to each of those functions whereas when Tom first made his proposal he was suggesting that there would be a recommendation relating to what institutions' responsibilities would be with respect to monitoring and what IRBs' responsibilities would be with respect to monitoring.

It is a way of slicing it differently but I just want to get a sense as to what you preferred.

DR. LO: Eric, I would agree with Diane and Trish on this point that conceptually it is much easier to think it through in function. After you do that then I think we do have to go back and say who does what but do not lead off with the how IRB should do this. Go back to the -- of the functions or issues that Diane and Trish --

PROFESSOR CHARO: I would actually go -- if I may, Tom, intervene and then I will get back to you. I would like to say that we should go one step further in areas like this and begin with outcomes, not even as functions, what are we

trying to accomplish. I think it comes through more clearly in the text than it does in the recommendations. In a sense I think the emphasis has been switched from what would make more sense.

If I were to make a list of the things that I think it is important we be able to do in the future, it would include things like knowing at all times exactly how many people are currently human subjects or human participants in research, including in minimal risk research. And knowing when their participation began and when it ended, knowing how many people had been injured, if any, knowing what compensation has been offered, if any.

In other words, we need to understand what is going on out there because one of the biggest problems we have had up until now is having a picture of the system.

And the second would be while the research is going on that the emphasis be on working during the course of the research to ensure that it proceeds according to its plan, the plan being one that had incorporated all of these ethical principles.

So the emphasis should be first on knowing what is happening and second on making sure that it happens the way it was intended to and that may involve all the tools that Diane has listed coming out of the text, and ultimately somebody has to say exactly how it is implemented and whose job it is, but every time we try to do that, we stumble on the fact that we are sending directions both for the enabling legislation and

for the ultimate rule making that follows from it. That is just kind of too many levels of government that we are trying to prefigure in our recommendations and so to some extent I want to just make sure we get our bottom line goals clearly out there.

Tom, and then Diane?

DR. MURRAY: Yes. I did not realize I was igniting a controversy over who -- how to frame the recommendations. I would say at the end when we finish the process we should -- the recommendations should be to particular bodies. That has a number of virtues. We have done it in previous reports and it will allow us to -- so that if somebody works at an institution they can look and say,"Okay, here is the bottom line for me, here is what NBAC is requesting or ordering that I do," or vice versa. And that is all I was proposing and trying to clarify.

PROFESSOR CHARO: Diane?

DR. SCOTT-JONES: I am thinking more about those various functions such as tracking changes to an approved protocol and I do not know how we would do that. I know that none of us would want protocol police who sort of go around and make sure that researchers are doing what they said they would do and to a great extent it depends on the researcher doing what he or she claimed would be done in the research so I agree with Tom that we need to say who would perform these functions because it is not clear to me how in the real world they would get done, although they are very important.

PROFESSOR CHARO: Bernie?

DR. LO: Alta, to go back to the question of what are we trying to accomplish, I would put at the head of my list knowing about serious adverse events, particularly those that were unanticipated, with a view towards making sure that the risk/benefit balance that was in the minds of the researchers and the IRB at the onset, still holds true midway through the study. So I think, you know, we have to go back to protection. We are concerned about some of the monitoring, frankly, I am not sure really serves the purpose of protecting human subjects to be blunt.

I get asked all the time, every time I change a telephone number -- I mean, the example that is thrown up is, you know, your area code gets split and now you are using a 650 area code or 415, you have got to go back to the IRB, they have got to read it into the minutes, and there are protocol variations, protocol deviations which are trivial, and I think part of the problem is that there is a sense that we focus on those and then we get nailed for those by OPRR and yet at the same time, you know, serious adverse events in big clinical trials go completely unreported.

So I would like us to really focus on the serious physical harms that really drastically change our assessment of whether it is ethical to do the research. Not to say that there are not serious problems of people doing stuff they said they were not doing, but I think data gathering just for the sake of knowing how people are involved, that is -- to me it is

only relevant. I want to know how many people are involved in the study is the one adverse event one out of a million or one out of three.

PROFESSOR CHARO: Eric and Tom, and then Trish.

DR. CASSELL: Well, I think that what Bernie said is basically right. We have certain things we want to know and yet it is not an all -- and yet what often happens is that monitoring becomes nitpicking and so forth. And so it is very difficult to specify a method because we do not know what the best method is. Sometimes the best method is just sitting down and hearing from investigators how is your project going and so forth and so on. So I think we should avoid specifying method.

I think what we should specify is which people or what bodies we are interested in seeing do this and what our basic interest is and also what our basic interest is not so that we not only have the one that is important that we are looking for adverse effects but we are not looking for bureaucratic details.

PROFESSOR CHARO: Tom, and then Trish.

DR. MURRAY: Yes. Thanks. It is good to have someone here with experience like Bernie's, both doing empirical research and serving on bodies that review it. I want to agree vehemently with him on two things and then disagree on one, which may not be material but let me start with the concept of material.

IRBs and the times of their members and administrators are scarce resources. That is simply a fact. The IRB is the

body -- if my faculty would have come to me and said, "Which committee do I serve on," and they wanted to serve on the IRB, I would point out to them that it is a terrific burden, that it is a self-sacrifice that one makes if you want to do it in most institutions and a very nice way to make enemies, and then I would say, "Sure, serve on it," but I want them to know what it was about.

IRBs are scarce resources. To force IRBs to spend time and to force investigators to spend time dealing with trivial things is pointless. In a way it trivializes the system, it makes people think of IRBs as paper shufflers. No one wants that. So I do not know if there is any way for us to institute or to encourage something like a standard of material change in a protocol rather than any change in a protocol.

Now how one defines that, how one decides -- who decides what is immaterial changes, but that would be, I think, a very welcome concept if, in fact, it could be applied.

PROFESSOR CHARO: Just as a point of information, the regulations already do make this distinction and there are changes that can be made without IRB approval and usually it is the administrator or the chair or both that make the determination as to whether --

DR. MURRAY: Thank you.

PROFESSOR CHARO: -- although there is some self-determination by the investigators themselves and how they portray things.

DR. MURRAY: Thank you. That helps.

PROFESSOR CHARO: Now whether or not it is working well is a separate question since Bernie's description of how it is implemented certainly does not match the intent of the regs.

DR. MURRAY: Right. So it may be that education would solve it rather than a change in the regs. Thank you for that clarification.

Now I want to speak briefly about adverse events. I will get out of the way what I disagree with Bernie on. I do not think it is the case, as far as I know, that certainly in any trial that falls under FDA jurisdiction, that adverse -- serious adverse events are not reported.

Even in the Gelsinger aftermath what we found was very disturbing. It was that the adverse events, I think, either entirely or almost all had been reported in the fashion dictated by FDA to FDA. The problem was -- there were two problems. One is that they were not getting reported to NIH as they were supposed to have been and NIH and FDA were not talking to each other about this.

I served on the oversight panel looking at NIH's role in this and, you know, I think the message was given clearly to both agencies that they really need to do this together. That said, I agree entirely with Bernie that one of the most important things that we can do is assure that information about adverse -- about serious adverse events, especially unexpected serious adverse events, is given in a very timely way to an appropriate body that can evaluate it to see whether

any changes need to be made in the protocol or any studies need to be, in fact, halted.

PROFESSOR BACKLAR: What we are really interested in doing is preventing the adverse effects, so what I am interested in seeing is what it is that we can put into our recommendations that the monitoring -- how we can affect the monitoring in such a way that the adverse effect does, indeed, not occur.

Marjorie and I were talking at breakfast about the issue of when you have people who have psychotic disorders and they are in a trial, and we know that people have fluctuating capacity. How can you monitor? How can you ensure that those people will be followed more closely so that if they start to have a psychotic episode you would know that they would maybe have to be looked after in a different way. I mean, that is just a small example.

So what is it? How could one think through as carefully as possible to make this monitoring work, in effect, before something occurs?

DR. MURRAY: That is not monitoring, Trish. That is protocol design. It is protocol design with feedback so that you get very, you know, quick and accurate feedback to the appropriate body, including the IRB -- which would include the IRB.

PROFESSOR BACKLAR: Well, a data monitoring board, in effect, does look at things. It does that. It looks to see how things are working to make sure something does not go wrong

because they are reading the material and the data and so on. And it seems to me that that is a model that one might want to look at and use in this kind of situation and I think somebody talked about tying the Data Monitoring Board into this in some way so that the information comes back. I think that would be very important.

PROFESSOR CHARO: We have now slid all the way into the next two recommendations having to do with adverse event reporting and I just want to make a -- it is very difficult to keep these things artificially separated. They are obviously linked so that is not a problem but I do want to make sure that there is some common understanding of the direction that we are giving the staff with regard to the next draft.

Is it possible to try and just go back and make sure that we have a common understanding of 4.5 all the way through now to 4.8, I suppose? Would it -- I mean, I am not even sure how I -- would you want to take a crack at this, Marjorie? I am not even sure if I could summarize it.

DR. SPEERS: Sure. I have heard --

PROFESSOR CHARO: What have you gotten so far --

DR. SPEERS: I have heard a couple of things. A couple of general things. One is that for the set of recommendations one of the things that we need to do in the text that then will fall out in the recommendations is to begin by clearly defining the functions and when we do the functions we will need to talk about the interrelationship of these various functions of monitoring. And then once we have defined

the functions to talk about who does what and then we can set the recommendations up accordingly.

Recommendation 4 -- and let me amend that by saying that as we are also talking about function as much as we can talk about the outcome, the purpose of the function, we need to do that as well so we know what we are after in these various types of monitoring that occur.

In 4.5 we need to break this recommendation down into two parts. One is what the central office should do and the other is what institutions should do if I captured that correctly. We would talk about those two separately. That may -- that may then involve combining 4.5 and 4.6 or the sentiment that is in those two to talk about what central office does and to talk about what the institution does.

I'm picking up -- I think another theme that I am hearing is monitoring is an activity that allows us to actually do two things. One is to potentially remove some of the burden now on IRBs where -- and that can be done -- at least we are proposing here one way of not requiring continuing review for all studies. The other is to focus on the important issues and issues that -- what I mean by issues are either adverse events or changes to protocols and so on.

The other piece of that, though, is to tighten up the monitoring where it needs to be tightened up, particularly when there are unanticipated, serious adverse events that would affect the risk and potential benefit analysis. So it is a

combination of actually trying to capture both of those principles, if you will, in these recommendations.

And I guess I do not have a clear sense of whether we have talked about 4.7 and 4.8 specifically or how those --

PROFESSOR CHARO: No, we were just kind of touching on them but we did not actually talk about them specifically.

DR. SPEERS: But that is what I have gotten so far.

PROFESSOR CHARO: Let me then open up the table both to additions to what Marjorie so far as well as comments on 4.7 and 4.8 on adverse event reporting.

Tom and Eric?

DR. MURRAY: Thanks, Marjorie. You are a very careful listener and a good synthesizer.

This is a minor point but I just need to signal it to everyone. What I learned in this experience at the NIH Oversight Panel on Gene Transfer Research was that terms like "unanticipated" and "serious" have well-defined meanings. Unanticipated, in particular, is a curious concept because in my description of potential adverse effects I include death, you know, parts of my body falling off. Then it is not unanticipated anymore. So we just -- whatever language we choose, we have to be careful because I think most of us would want to know that and think that the IRB ought to know that because, even if it was anticipated that it happens in this particular design or that it happens at a certain frequency, could be absolutely vital information.

PROFESSOR CHARO: Eric?

DR. MESLIN: Mine is just a matter of focus. After all, what you are writing here are directions for a central office. If we stop and say, well, now you are the new boss of this central office and you have got this detailed set of recommendations, it is more than likely that you would not pay much attention to the operational details that are here but to the general mandate for monitoring and reporting adverse effects and so forth.

The real emphasis of all of this is that this is now a central concern. It is -- and that it is to be carried out through the direction of a central office of some sort. So I want us -- I should think we should not get too caught up in how anything particularly should be done but make it clear that we are trying to mandate something for the future.

PROFESSOR CHARO: Bernie?

DR. LO: Yes, I agree with what Tom and Eric said. Just stylistically, although I certainly agree with Tom that, in the final analysis, the recommendations have to be tied to who does what, I am a little concerned as I read them through it is a lot of central office issuing regulations. And I just think we need to make it clear that is not the main thing we are trying to do. It is language like the central office should continue its current efforts to better coordinate among FDA, NIH and local IRBs the reporting of serious adverse events, particularly unanticipated, just to kind of phrase it in a different language.

PROFESSOR CHARO: Other comments?

PROFESSOR BACKLAR: Also in the style. I think it would be good to go back and look at the capacity report and some of the other reports where we cluster things under particular headings. I presume you are going to do that.

PROFESSOR CHARO: I would add only specifically to 4.7 and 4.8, which focus on the adverse event reporting, something that I think may be -- maybe it is implicit in some of the other comments but since we are anticipating the use of designated IRBs more frequently, I would like to here emphasize something that Bette was emphasizing there, which is that where protocols are being carried out in multiple sites, an essential part of the protocol design has to be some anticipation of how adverse event reporting will be managed, in order to assure that the full pattern of adverse events is visible to whoever is watching for them. All right. That just would be one of those essential parameters that maybe should come up in this recommendation or the other one. I am not sure.

Bernie?

DR. LO: Alta, along those lines in 4.8 where we talk about the responsibilities of sponsors, I think the role of the sponsor is really to assure that, in the protocol they are sponsoring, there is a usable plan for reporting adverse events. I do not like the verb -- whatever it is -- streamlining because it is not so much the streamlining of reporting, it is to assure mechanism for timely and accurate reporting.

And it is not so much they develop the mechanisms as they assure that it is in the protocol because they may rightly say we had the principal investigator and the DSMB chair work out how they are going to do it but we are saying that is true but you have got to assure that it is a feasible system.

PROFESSOR CHARO: Other comments?

Okay. I think we have kind of -- oh, Bernie, sorry. Go ahead.

DR. LO: It is along 4.8. Reporting analyses to all parties involved in research, I think that has to be as appropriate because it may not be appropriate to break the blind or to tell every participant of adverse events where you are not sure it is a trend.

PROFESSOR CHARO: Tom?

DR. MURRAY: There is one more key concept in the FDA definition or the reporting requirements that is associated and that is, was the adverse event believed to be associated. That is also a critical one. We are going to have to decide what, if anything, we want to say about that. It was pointed out in many of these gene transfer human trials it is anticipated that many of the subjects will die because they have got a lethal disease and they are near death anyway. And so it is a key to find out which of the deaths are worsened or hastened by the treatment, rather than simply a consequence of the disease itself, but we just have to wrestle with that.

PROFESSOR CHARO: Well, you know, at the risk of bring something up just at the moment at which I thought we would be

breaking, a perennial dilemma for IRBs has been deciding when the information of current participants and prospective participants will be given ought to be changed, and there is that difficult problem of information that is not statistically significant but is suggestive enough that now all the people who know about the information are watching it very closely to see if it will move to the point of statistical significance.

And there is a very basic question about entitlement information that underlies this and underlies the informed consent process, whether that process is one in which people are entitled to be informed about information that is considered to be scientifically valid by which statistical significance is usually implied, or if they are entitled to be given all the information that they might want. And we know from experience that people often want information even though it is not yet validated but is merely suggested.

Since we are focusing so much on the adverse event reporting, I would put out on the table that this is an opportunity if we want to take it to say something about this. Not because we need to set a rule but because guidance on this point is the kind of thing that would have a significant effect on IRBs all across the country since it is a problem that crops up repeatedly for them.

DR. LO: Alta, I totally agree. I think it should go on our list of things that need to be thought through just as Tom's point about what is associated with the trial and not -- these are things that we should just say these are the kinds of

issues that need to be sorted through but it is not an attempt to get into it because that is a huge, huge -- and actually a very technical discussion as well, and I just do not think we are the body to do that.

DR. MIIKE: You were going to call for a break but I think 4.11 properly follows all of this discussion and it should -- 11 is really about the suggestion about a system of compensation. So if we can discuss it now or after the break.

PROFESSOR CHARO: I agree that it follows but I think it follows the break.

DR. MIIKE: Okay.

(Laughter.)

PROFESSOR CHARO: Jim, you have the last word.

DR. CHILDRESS: Oh, it is about the compensation so if you want to take a break --

PROFESSOR CHARO: Yes. I think it probably makes sense just to make sure everybody is fresh for a conversation that has been going on for 25 years.

Why don't we come back at 9:45 and we will reconvene?

MS. KRAMER: Will this be the last break before lunch?

PROFESSOR CHARO: It is not a bad idea to checkout. We might take a quick one at the end of 4 before we go on to the remaining issues in Chapters 2/3.

(Whereupon, at 9:30 a.m., break was taken.)

PROFESSOR CHARO: In order to save perhaps about 45 minutes ideally at the end of the meeting to discuss some lingering issues from Chapters 2 and 3, particularly with

regard to vulnerable participants of research, it would be great if we could move through the topics that remain here in the course of an hour-and-a-quarter to an hour-and-a-half.

And they encompass several that might be worth some serious discussion so it makes sense then to move on to recommendation 4.11 and the perennial bug-a-boo having to do with the compensation.

Jim, you had wanted to make a point on this.

DR. CHILDRESS: I thought Larry would say how disappointed he was that this was back in and I was going to rejoice that it is back on the table.

(Laughter.)

DR. CHILDRESS: I like the recommendation but also the question that Larry raised about where it should be put, assuming that it is kept. It does sort of jar just looking down the list of the recommendations and the current placement. On the other hand, the argument in the text on page 29 about why we ought to return to this topic that has been around for a long time and never really has been resolved, is a reason that focuses on the concerns that institutions raise about relying on external IRBs so the logic of it does follow that and so I can see a case for keeping it here. On the other hand, Larry is right that it really has to do with the question of compensation for the injuries and illnesses that are associated with the research. But I am glad to see it here and I like the direction of it.

PROFESSOR CHARO: Larry?

DR. MIIKE: Well, in the interest of time, let me just say that this seems to put the cart before the horse in the sense that we just talked about how we need to get better information on adverse events and monitoring systems, et cetera, and then we end up with a thing that says let's pass a system of no-fault compensation and, by the way, we will ask the agencies for the data for it.

You know, I have had experience with the swine flu vaccine compensation, the vaccine injury compensation, and then the early days of the vaccine research trying to anticipate these kinds of issues. It is a morass. And I am not adverse to mentioning this as a possible compensation for people injured in research, but I cannot really support moving forward with legislation on this until we really know whether there is a problem that requires us developing a whole system. And at any rate that is why I think it should really follow after the recommendations on monitoring and adverse events.

PROFESSOR CHARO: Jim?

DR. CHILDRESS: And again I would argue strongly for the location where it is. I think there is a reason for putting it here but I could easily go with Larry's direction. I guess I am not convinced that we need to know a lot about the extent of injury before actually making a recommendation for no fault compensation system. Clearly the extent will have a bearing on how well such a system can function and the like.

But one particular thing about our context that I actually think does need to be mentioned in the text, and when

we had the meeting -- the international meeting in San Francisco, one of the reasons it was clear that compensation was not so much an issue in any other context, is that there is not universal right to health care in other contexts. That is an important part that we do not have that that makes it then real important to build in compensation for research related injuries.

PROFESSOR CHARO: Bernie?

DR. LO: Bill had his hand up first.

PROFESSOR CHARO: Bill?

MR. OLDAKER: Go ahead, Bernie.

DR. LO: Again I very strongly support that people who are injured in research should not be financially harmed in addition to whatever physical and psychosocial harms they suffer, particularly if it means having to pay for medical care.

So I think as a general principle of supporting fair, adequately and timely compensation, I can get behind that. I just do not know enough about a no fault system versus whatever other options are out there and so I would be very wary of backing a specific proposition in light of what Larry said.

PROFESSOR CHARO: Bill, and then Eric Meslin.

MR. OLDAKER: Two points. One a small point. I probably -- if you are going to talk about liability, I would disengage that from the data collection. I think that Larry makes a valid point that, you know, two things -- it looks like you are putting the cart before the horse. But I think if you

are going to do -- so I think data collection is probably not essential to making this recommendation if that is what people desire to do.

I do not -- I have a different issue. I am actually in favor of a no fault system as long as it does not impair the other rights of the person who has been injured. I do not want to see us recommending something that would limit a victim's rights to file a lawsuit to recover punitive damages, whether there has been neglect of a great sort to that person. In other words, right now if we had a no fault system, the case in Pennsylvania, the Gelsinger case, whatever it is, he would not have a right to file a lawsuit which asks for punitive damages.

So I think that having a no fault system that does not impair other rights I could find -- I could accept and I think we just need to be very careful not to do that.

PROFESSOR CHARO: Tom?

DR. MURRAY: Yes. I am wondering about the intersection of public and private here. The --

PROFESSOR CHARO: Closer to your microphone, please.

DR. MURRAY: Yes. For publicly funded research I think a no fault system makes sense and you have some sense of who would be paying into the system and how it might be adjudicated but where you have got this, you know, research -- clinical research, in particular, is moving to private funding and so, in many cases, the research sites are not themselves even academic health centers so I am not sure how it would work and how you would -- unless -- I just do not know the mechanism

of how you would develop a system that would include some help, both the public component and the privately sponsored component is more complex than my mind can get around at the moment.

PROFESSOR CHARO: Eric?

DR. CASSELL: Well, I want to endorse that and move a step further. I think it is premature to say what kind of system. The basic statement is that we believe people injured in research should be compensated and the details of how that should be best done and how we handle private and all that kind of stuff, I think, is not for us to decide at this time. There is not data and there are many other things to resolve.

PROFESSOR CHARO: If I can put in my two cents here. We have finally gotten to something I actually know something about since I teach torts. I strongly endorse the idea of backing away from a specific recommendation. There are many versions of no fault systems. Some would cut off other legal rights, others would not.

There are administrative systems. There are external review boards. There are the creation of presumptions that can be operative in the ordinary tort litigation. There are myriad systems by which you can facilitate recoveries. I agree strongly that the most important statement that can be made is that compensation is appropriate.

The one thing I would add to that statement is that we should tie it to our notion about causality because this is an area in which there are many people who have many bad outcomes, that are not caused by the research intervention, but are

caused by the underlying illness. In a more complicated fashion, however, the outcomes are often caused by a combination of the two.

The thing that is a moral judgment that underlies what in law would probably be called proximate cause, is what our stance would be with regard to those outcomes that are due to the combined effects of somebody's underlying conditions and the research intervention.

Courts are all over the place on how to manage this kind of problem where you have got multiple causes that together, or in sequence, lead to a single injury and it can either result in no compensation being permitted, or in full compensation being permitted, or in partial compensation being permitted. And there is a kind of value judgment that underlies that decision, and if we could get some guidance on that, in conjunction with the statement that compensation as a general matter is appropriate, I think we -- given the key things that are needed and then somebody else can decide whether the best way to implement it logistically is through the existing tort system, through administrative mechanisms, through no fault,et cetera.

Larry?

DR. MIIKE: I can support the notion that Jim mentioned on this and I would not use the word "compensation" because it starts getting into monetary damages and gets into the whole tort area but I think we can make a principle statement that people involved in research -- because we make

it in the international report about health care continuing to those and I think we should have a parallel statement here. That I could support.

PROFESSOR CAPRON: Hand up.

PROFESSOR CHARO: Yes. Is that Alex?

PROFESSOR CAPRON: Yes.

PROFESSOR CHARO: Welcome, Alex. Please.

PROFESSOR CAPRON: Okay. I believe we should address the issue. I believe that the term "compensation" is appropriate. I am just going to go through a list of things. I do not agree with the division -- the use of the language on page 32 of direct and indirect costs just because that gets at the language which in the compensation area is used to mean something different for historical reasons and I think we should just say medical costs and other costs such as loss of wages. In no fault compensation it is not typical to provide for so-called pain and suffering, which is really a surrogate for other things in any case.

I think we are talking about something which is a nonfault system. In the fault system because you have an injury caused by negligence the issue that Alta raised about other conditions or even other causes that bring about the injury is usually resolved by making the tort user liable, even if there is some other reason, and so to use the language that is often used, "you take your victim as you find them," and the person with a so-called eggshell skull, someone who would be injured by a slight injury in a way which is much more severe

than a person who is healthy, is entitled to compensation for the injury that they actually suffer but that is because the person starts off with an injury that is caused by negligence.

Here we are assuming that, what is needed is something which addresses situations in which there may well not have been negligence but rather the desire of the person who suffered arises from their willingness to advance science by being the experimental subject. And I think that most of these -- you know, the intellectual argument as to why it makes sense to do that have been spelled out in prior reports, which are -- to which some reference is made here.

I think I agree with Larry that it may be better if what he was suggesting is that this should be in Chapter 3 as one of the ethical issues of protecting human subjects. It is possible to see it there. It does not directly relate to most of the things that are addressed around IRBs in this chapter, but if most people agree with Jim that it belongs here, I certainly do not disagree. I do not feel strongly about it.

I would separate out the two sentences in the recommendation 4.11. It seems to me that we ought -- the first sentence of enacting a system of no fault compensation is appropriate. And then the second sentence should be that the system should be -- the effects of the system should be monitored and reviewed based upon data collection. We do not have any advance on this issue over the last twenty years because since the recommendation in 1982 that an experimental system be set up, it hasn't been done by the Federal

Government. So we -- I think we do have greater evidence that there has been more harm in research in the last twenty years, as there has been more research, and it apparently involves riskier things than there was before that time, and obviously the Gelsinger case is a strong example of the risk.

So I am in favor of the recommendation and I am in favor of dividing it into two parts and I do not really care which chapter it is in.

PROFESSOR CHARO: Other commissioners?

DR. MIIKE: Well, Marjorie, you have clear direction.

PROFESSOR CHARO: I think -- no, I think it is very -- I think it is implicit in any system that we are going to implement here that we are anticipating an abandonment of traditional negligence concepts because they would not work well in the context of research because there is no standard of care with regard to these investigational interventions.

PROFESSOR CAPRON: Right.

PROFESSOR CHARO: I am talking now on the biomedical model.

PROFESSOR CAPRON: That is correct.

PROFESSOR CHARO: Right, but whether it becomes a no fault system, as in vaccines, or if it is simply the replacement of a strict liability standing with a negligence standard or some other mechanism I do not know, is really within our capability to do sensibly at this time but if we can ask the staff to redraft slightly and try it out again before

our next meeting at and at our next meeting we can try to flesh it out a little bit further.

PROFESSOR CAPRON: Alta, one other comment. I think we may want to use the phrase "nonfault." "No fault" is specifically attached to the automobile compensation system adopted in many states and it is actually a system based on first party insurance primarily. That is to say you insure yourself for the harms that you might suffer. It is a slightly different situation than this.

PROFESSOR CHARO: Yes. We might try that or something that simply says that it is not based on negligence and see --

PROFESSOR CAPRON: Exactly.

PROFESSOR CHARO: -- even strict liability has a fault component and that might be where we want to wind up but let's leave this for a next go around because I think this one actually needs more focused attention than we can give it right now. I think we have got the basic thrust.

Let's move on then to 4.12 having to do with the composition of IRBs. This recommendation represents a departure from the current approach. Some degree of departure and reactions would be welcome.

Tom and Bill? Alex, did you have a comment on this one as well?

PROFESSOR CAPRON: No, I do not.

PROFESSOR CHARO: Okay.

DR. MURRAY: I propose that it should read regulations requiring majority of IRB members not be affiliated with the institution.

PROFESSOR CHARO: Oh, he is going for broke.

Bill?

(Laughter.)

MR. OLDAKER: I was going to say we set forth a percentage but I can live with the majority.

DR. MURRAY: Let me note that would not make us an outlier. That would actually probably bring us more into conformance with how much the rest of the world composes their own IRBs.

PROFESSOR CHARO: Just as a point of information. Denmark does this. Is there any other country that has a majority?

DR. MURRAY: New Zealand does.

PROFESSOR CHARO: New Zealand.

DR. MURRAY: Those are the only two countries that have majority.

PROFESSOR CHARO: Okay. But they are wonderful countries.

(Laughter.)

DR. MURRAY: They are wonderful countries.

MR. OLDAKER: I would suggest that we set forth the percentage that we like so that at least there is some uniformity.

PROFESSOR CHARO: Other reactions to this proposal which is now a significant departure? Bette?

MS. KRAMER: I am just curious how it is going to work out practically in terms of how institutions are going to get these people.

PROFESSOR CHARO: Other comments?

Tom, would you like to put forth the argument for it? I do not know if silence equals assent or silence equals stunned.

DR. MURRAY: I was going to guess stunned myself. Well, right now we are -- the current language is fairly vague. It just says "requiring a greater percentage" but it does not say what. The greater percentage could be .01 percent greater and that would satisfy the sense of our recommendation. IRBs ought to represent broadly, I believe, the community of people who will be the participants in the research.

Right now it has been -- I mean, there are two knocks against IRBs, the current composition and placement, and we are just dealing with the first of them here. One is that they are dominated by researchers and they are dominated by institutions. The second is that they are the creatures of the institutions who in many ways stand to benefit from having the research go on at their institution.

Now we have lived with that and that is a conflict of interest. It does not mean -- it does not make it an evil conflict of interest. It simply is a conflict of interest.

To have broader public representation on the IRBs, what I think make them more accountable and more responsive to the communities and to the population, to those people who are likely to be participants in research. I think the argument is straightforward. I think the opposition to it -- I can imagine two counter arguments.

One being, well, they are not going to be experts. That is true but most researchers are not experts in a goodly number if not the majority of protocols they are asked to review.

And number two is there would be difficulty in getting people to give this amount of time to this kind of activity. That seems to me to be a more relevant obstacle but one that could be solved in a variety of ways, both involving whom we choose to be IRB members -- to be members of IRBs and/or whether we can offer them any compensation for their participation.

PROFESSOR CHARO: Jim?

DR. CHILDRESS: Tom, I think you are making the assumption that these would be public members but there is nothing in the recommendation that says that and one could have a situation like Charlottesville where there is a second hospital, for example, and there are a number of researchers there who can serve on the University of Virginia's IRB. So if we want to limit -- if we want to make this public members then we need to say so.

PROFESSOR CHARO: Indeed, by way of request for clarification, if I may, Marjorie, the recommendation as it stands talks about a greater percentage of IRB members who are not affiliated with the institution, which at first I read as being public members who were nonspecialists in either social science or environmental research. And then I read it more closely and thought, no, actually this is probably about conflict of interest and the idea is it should be people who are not affiliated with the institution within which the research is going on.

And then I realize I did not know what actually was the intent here. Was it to get more lay people on the IRB or more people who are free of the conflict of interest problem? If it is the latter then I was not sure how this would work with the so-called independent IRBs that have no institutional affiliation. So if you could start us off by telling us what the intent of the recommendation is maybe we could figure out what we would like to see ideally.

DR. SPEERS: I will tell you actually two things. One is the intent of the regulation was to deal with conflict of interest. The institutional conflict of interest that occurs when a predominant number of the members on the IRB come from the institution.

The second -- the reason that it, in part, is worded the way it is here, is it comes from what is used in the current regulations where the current regulations require that

an IRB have at least five IRB members, one of which should -- must be unaffiliated or not affiliated with the institution.

The current regulations do not speak to the issue of public members or community members. Those are terms that have, you know, developed over time and what the unaffiliated member has come to represent.

PROFESSOR CHARO: So let me put the question out then because there are two separate questions. What is our sentiment? We do not have to be bound by anything in the current regulations. We are working in the land of the future. What is our sentiment with regard to lay persons and what is our sentiment with regard to people who are free of institutional affiliations that are shared by the investigator? I think it is probably the pertinent thing since with independent IRBs there is no institution to speak of.

Trish and then Larry?

PROFESSOR BACKLAR: I was interested that we did not address the issue of taking the "I" out of the IRB and we had all these people speak to us at our last meeting with very creative ideas, particularly the Denmark model. We addressed this a little bit in our discussion but not very much and I, for one, would be very interested in exploring that and in exploring that looking then at the composition of the IRB in that model.

PROFESSOR CHARO: So, Larry?

DR. MIIKE: If you are talking about lay members being outside and institutional members being those with the

technical expertise, to me the issues about conflict of interest are more important in that it is the institutional members. I think we have heard about colleagues being hesitant to criticize colleagues, and so I would not want the emphasis to be heavily on the lay side, but also in the internal side so that we can have true scientific review of these proposals.

PROFESSOR CHARO: Bette?

MS. KRAMER: I am really not prepared for this because I missed the last meeting so I do not know what those presentations were, but just thinking about it practically, and thinking about my husband's experience when he was chairing the IRB at the community hospital in Richmond, yes, Jim, there are other hospitals in Richmond. He found there was enormous difficulty getting people from within his own institution to serve on the IRB and to be reliable in terms of this service, let alone trying to go outside to other institutions.

And to the extent that we are talking about research being conducted at multi-sites as opposed to single sites, you can have more and more people, more and more institutions who are going to be community institutions and faced with this kind of problem. And as I think about it, I am not absolutely certain but I believe that the lay person that they were able to get to serve, in a sense he probably had a connection with the institution as well as he was the person who customarily did volunteer work at the institution.

But it is very, very difficult for a community institution to go out into a community and to find people who

are unaffiliated with the institution who have sufficient background to sit on an IRB who care and are going to, you know, have some commitment to showing up.

Now when we get into Chapter 5, if a part of what we specify there is compensation, maybe that will change the equation. I really do not know.

If what is driving this recommendation is conflict of interest, maybe there is another way of addressing conflict of interest other than this.

PROFESSOR CHARO: Bill and then Eric?

MR. OLDAKER: I think conflict of interest is the central thing to worry about here and to try and solve. I think that compensation Bette touches on has to be -- you cannot have these IRBs, at least in my estimation, as voluntary organizations and expect them to perform all of the things that we are laying out for them and the fact that we are going to say that they are going to be certified, and they are going to at least place themselves in a position where they can be embarrassed.

I think, you know, you will not find many people who are willing just to volunteer a great amount of time outside of the institution and probably even inside the institution so I think the two things have to be tied together.

One, you have to figure out how to compensate people in some way and, two, you have to figure out how to make the board more diverse. I am not sure what the percentage is but a

higher number of people outside of the institution who would be on it that would grant it some ability for affectivity.

As far as independent review boards, the for pay review boards, I would think that they would all be noninstitutionally based to start with so that takes care of that problem.

PROFESSOR CHARO: Bernie?

DR. LO: Yes. I just want to throw in an argument for not losing sight of the lay members as opposed to the unaffiliated members as far as conflict of interest. In the -- in previous reports, particularly the impaired decision making capacity report, we pointed out that people, who are like the potential participants in research or family members, can often tell you things about what it is like to be in such a protocol, what it is like to go through that informed consent process that are just not obvious to someone who has not been in their shoes, and we actually encourage IRBs to add expertise so they can really understand the point of view of the participant because their concerns just may not be addressed.

So I think there is a role for both lay as opposed to scientific members and nonaffiliated as opposed to institutional members which is I think the current, you know, scheme in the CFR.

PROFESSOR CHARO: Eric?

DR. CASSELL: My experience when I was the chair was, at the first couple of meetings, the new IRB members were pointed out all the difficulties of doing research with all

these regulations and by the third or fourth meeting they were deputy sheriffs, and my own sense is that the education of IRB members is more crucial than it is where you get them because I think there are real difficulties to getting at people from outside the institution. I think it should be a recommendation but I do not think it will work as a requirement.

PROFESSOR CHARO: I would only share from my own experience the following observations that lay members, as in Bernie's experience, have often been able to perceive ambiguities in the protocols or areas of confusion that the more technically literate people cannot but that because frequently the lay people are tokens on what is otherwise a very large committee made up of credentialed experts, they do not participate as assertively as the others.

And that, for that reason, a somewhat larger number of lay people is often important, just to make it possible for any one lay person to feel empowered to speak, which is an argument not necessarily for going to a majority of lay people, but to go into something more than the token system we now have often seen implemented in IRBs in which the lay person is the unaffiliated person and there is a correspondence between the two.

The second is that the conflict of interest that is created by common affiliation is real. I have been impressed at how well I have seen people manage it. I can only speak for one IRB I have worked with in any depth, so it is rather self-serving, but I have actually seen it overcome on a regular

basis. But I do fear that in the current transformation of medical school funding for education, that the pressures are going to increase in ways that are going to make it more and more difficult to overcome that conflict of interest, in which reviewing people from one's own department or one's own division has a financial effect that is felt throughout the department, or even the division, and makes it ever harder to really be dispassionate.

It may be that we want to call for some increase in the combined number of unaffiliated and lay persons in order to diffuse these tensions somewhat in both directions. I do not yet hear a kind of majority support for Tom's majority proposal but it is still on the table.

Marjorie and then Tom?

DR. SPEERS: Just before you make suggestions for recommendation, what I would encourage so that we can be clear as a commission is, I believe when you are using the term "lay" you mean a nonscientist. Is that correct?

PROFESSOR CHARO: I mean -- well -- or it could be a nonscientist or a nonsocial scientist. I mean, a nonexpert in the areas that are the subject of research being reviewed.

DR. SPEERS: Okay. I just want us to be clear, because on the terms of nonaffiliated members individuals who represent the participants and nonscientists or nonexperts in the area of research being reviewed. Because I think that those three get -- terms sometimes are used interchangeably and get convoluted and it sounds like you want to make

recommendations that may relate to all three of those types of people.

PROFESSOR CHARO: Tom?

DR. MURRAY: Thanks, Alta.

Let me begin just by summarizing what I think I have heard thus far that having people who are unaffiliated helps respond to the problem of potential conflicts of interest, that having people who are not themselves engaged as researchers, but are more representative of the people from whom participants would be drawn, would provide perspectives that otherwise might not serve us and that could be very important considering the ethics of any particular research project. So it seems we probably want to do both of those things better than they are currently being done.

The other thing I want to mention is -- I am going to -- I am offering this as a rebuttal to one of the potential objections to having more outside members, and this would go to whether they were lay or chiefly noninstitutional, and that would be the cost that somebody would have to pay them. Well, in fact, it is quite possible that it would cost an institution less to do it that way than it would to try to draw from the ranks within. Simply take into account the concept of opportunity costs. If a very talented clinician is giving up half days or one day a week in clinic to be in the IRB, that is a very substantial cost to the institution. Now to the individual, if a talented researcher is spending time in the

IRB, rather than generating proposals, that is also a fairly substantial opportunity cost to the institution.

Now the money may not get -- the cost may not get allocated very sensibly in all that. I recognize that but I mean a wise institution would -- should at least take that into their analysis.

PROFESSOR CHARO: Bernie?

DR. LO: Just as a cynical response to Tom, you are absolutely right that the cost accounting is very diabolical. I bear the costs of my committee work, not my institution or department. So it costs the institution nothing. I just have to make it up some other way.

DR. MURRAY: That is until you leave out frustration.

DR. LO: But anyplace else I go I will suggest I will have the same problems.

PROFESSOR CHARO: Let me do -- because it is awkward, Alex, did you want to intervene here?

PROFESSOR CAPRON: Well, I think several of the points that have been raised deserve further discussion. I think Tom actually is right that we could take note of the opportunity cost. The fact that, as Bernie said, only some of the costs are modified on the institution's books, is just a way of emphasizing something I think we are saying throughout this report, which is that the process of research oversight legitimately is a part of the cost of doing research and ought to get more support.

And the notion that you cannot ask people, without institutional affiliation, simply out of loyalty, to do what those who have institutional donations do in terms of giving up their time means it is appropriate to pay them. I do not think -- I disagree with the language in here. This calls into question their independence. There are many people who are paid to do jobs in which they are expected to act independently of the person that pays them. And I really think that if we mention that as a concern we ought to answer it. I do not think it is a concern.

As to Tom's basic proposal that we say it be a majority, I think that the greatest argument in favor of that is it makes the whole recommendation be taken seriously. I suspect that the AAMC and the AAHC or whatever else, the organizations, that we would -- the health centers and the medical schools will lobby very heavily that that is too much to expect them to be able to do.

The fact that we do not now have a percentage, we have an implicit percentage of 20 percent. I mean, 16 percent, I think. It is either -- it is one out of five or one out of six.

DR. SPEERS: One out of five.

PROFESSOR CAPRON: Then it is 20 percent. But, in fact, as we know, many IRBs are larger, without increasing the relative proportion, and I believe that the regulation, that if an institution does that they can get an MPA without a problem, I mean, if they have a 20 member panel and --

DR. SPEERS: Mm-hum.

PROFESSOR CAPRON: Isn't that correct, Marjorie?

DR. SPEERS: Yes, that is correct.

PROFESSOR CAPRON: We do not have data that tell us what the composition is, to the best of my knowledge, that is to say there are not reports on what institutions actually do but I think we all know from the anecdotal experience that some institutions are close to 20 percent and others are probably a little bit above and others are way below.

Not just for saying a greater percent or specifying a percentage, I think is an appropriate approach and we might want to separate out those two ideas and say that the percentage should be set and then say the percentage should be set at 50 percent or greater.

I have a sense, as I say, that in the efforts that will go into OHRP's eventual disposal of our recommendations that it will be likely that the first part saying that there should be a set percentage will go farther than it should be 50 percent, but we will get a lot more discussion of the topic and a lot more focus on the reason that unaffiliated members help to support the goal of independence and not an avoidance of institutional self-interest and bias by being dramatic about it.

So if you need a second for Tom's recommendation, I would not have made it, but once the arguments are put forward I think for rhetorical, as well as policy reasons, it has a lot to recommend it.

PROFESSOR CHARO: Bette and then Arturo?

MS. KRAMER: I guess I am particularly sensitive when you start talking about the public members. I am not sure why a public member could not be somebody who comes out of the sciences, particularly somebody who comes out of the social sciences. I do not see any reason for restricting that.

It seems to me as a matter of fact a person like that might be more interested in serving.

PROFESSOR CAPRON: Oh, I think that is -- Bette?

MS. KRAMER: Yes.

PROFESSOR CAPRON: I do not know if you were responding to me.

MS. KRAMER: No.

PROFESSOR CAPRON: I think the issue of lay -- that is to say not a scientist dealing with the field of research that this committee looks at and we have to recognize there are IRBs that just -- that only do social science and behavioral science research and a physician is a lay person in that panel.

So, I mean -- so I think the issue of the lay issue, not that field of science, and the unaffiliated are separate.

I agree with you, if that is what you are saying, and I can well imagine that you could have a physician from another institution, or from the community, or a social scientist, or whatever, who would be unaffiliated with the institution and bring a view that is independent of the institution's own interest to bear.

PROFESSOR CHARO: Bette, did you want to continue?

MS. KRAMER: Yes.

PROFESSOR CAPRON: So I agree. I am sorry to interrupt.

MS. KRAMER: Okay. That was one point I wanted to make. Another point is that I think it is unrealistic and unfair to consider that the lay people are going to have any -- are going to have any impact on conflict of interest problems unless you are envisioning getting an accountant or some specific person like that who is going to look over things. But, you know, I just -- I think that that is probably unrealistic.

I do think it is very, very important that there be multiple people because I think it is very difficult for one person alone to feel empowered and I think that that is terribly important.

PROFESSOR CHARO: Arturo?

DR. BRITO: In principle, I agree with Tom's suggestion for majority IRB members to be outside the institution but the biggest concern I have -- I think at institutions such as the University of Miami and the University of Wisconsin, where they have a lot of other resources to draw from and creative means of coming up with ways -- not around this, sort of through this really -- for instance, in a big city like Miami you can draw -- there are several other institutions.

You could draw members from different institutions to represent them and back and forth can be exchanged in that way.

And there are people in the lay -- there are lay -- lay representation is usually not a problem. We have a retired pediatrician that serves as one of the lay members on our IRB.

My concern is more at the smaller locales. Community-based organizations are doing more and more research in small towns in this country that would be unable to come up with a majority organizations because they do not have the resources. So in theory, I am in favor of this, but from a practical point of view who would be hurting the most here is the small communities often representing the more vulnerable populations. So I just am a little concerned about that.

PROFESSOR CHARO: Larry? And then I would like to try to see if we can give some coordinated direction to the staff.

DR. MIIKE: While I sympathize with the small community, small institutions, my guess would be the pressures of conflict and acquiescing to research is even greater there because their community is a lot smaller than in the large institution. So there is that side to it.

PROFESSOR CHARO: By way of trying to come up with a summary here, it seems to me that there are certain underlying values in the decentralized research review system that are now not completely coordinated -- that are somewhat in competition with one another and it may help to get some sense of the prioritization of those values.

One has to do with the ability to perform reviews at the most local level possible, since Arturo's point about the resources of community hospitals is well taken, and we want to

encourage them to have their own research review boards as opposed to relying on an external board, such as an independent board, so any requirement with regard to their membership is likely to be difficult to manage.

If the priority instead is in simply making sure that there is no conflict of interest between the reviewers and the reviewee, the financial or personal, then the focus needs to be instead on making sure that a sizable number, if not a majority of the reviewers, have no personal or financial interest in the outcome of the discussion, and that would mean that independent IRBs are already fully meeting those requirements.

Whereas the institutionally based IRBs would now have a major challenge ahead of them. A challenge that would get more and more complex as institutions merge and create affiliations that would string the definition of institutional affiliation.

If the point is to make sure that the research endeavor has obtained the public's trust, then the argument can be made that you need more people who are not themselves representative of the research community, but instead are representative of the likely participant communities, because if they sign off on something then they are acting as proxies for the people who will eventually be recruited.

It is not possible to do all these things with review boards that now approach 30 and 40 members, which is unwieldy for all sorts of reasons, even putting aside the resource question.

Do we have a sense of the priorities? The order in which we care about these things? Because that will drive, to some extent, the suggested requirements that we make for the research review boards in the future.

PROFESSOR CAPRON: Hand up.

PROFESSOR CHARO: Your hand is up.

PROFESSOR CAPRON: Okay. Three quick comments. I do not see the one conclusion that you drew there about the size of the board. Obviously people can wear different hats and you can get a group that is a lot smaller than 30 or 40 who does what you need to have done.

Also, many IRBs find themselves facing research protocols that involve technical issues and they bring in a consultant, somebody who knows about the issues that are raised, whether it is directly in the research or, you know, an expert in kidney function because someone is concerned that the research might pose a risk even though it is not looking at kidney disease or causing kidney disease. And I think that that sort of thing can keep the numbers on the IRB down.

I think we should go to the literature, Marjorie, on small groups. There is a lot of literature on small groups that talks about the problem of the single person in a small group or even the minority, let's say two out of 15 or something, who have a hard time exercising any influence on what the group does.

I do not think, Arturo, that the smaller communities are the problem that you describe. Those communities are able

to find plenty of talented people to serve on school boards and PTAs, on church boards, on other civic organizations, and the very fact that the community maybe has particular interest, or characteristics, is all the greater reason for making sure that it is well represented in the board, the IRB, for all the reasons that I think Alta just mentioned about community trust in the sense of assurance, that when a project is out there, it has been well vetted with people who are, in effect, drawn from a potential subject group.

We talked about this in other reports even to the point of saying in certain populations we have to make sure that they are among the IRB members and are present at the meetings. And that is actually something which is not addressed in our recommendation here but the presence of these noninstitutional members at a meeting, it seems to me, becomes essential.

PROFESSOR CHARO: Arturo and --

DR. SPEERS: It is in the recommendation, Alex.

PROFESSOR CAPRON: It is?

DR. SPEERS: Yes. The presence of these members --

PROFESSOR CAPRON: Oh, yes. I am sorry. You are right. It is there. I am sorry. It is right. It is there.

PROFESSOR CHARO: Arturo and Tom?

DR. BRITO: If we are talking about the majority of representatives that are still going to be mostly scientific experts -- right? We are all in agreement with that. They are just not going to draw -- and have majority representatives

from the lay public. Is that correct? Is everyone agreeing with that?

My concern here is that there are -- I worked in a small town in Alaska in a remote village -- in a remote area in Alaska and if you do not allow the one institution that provides the health care there and you are going to draw from the -- you are -- there is no other -- there was one other physician in there that was not associated with the institution in that entire community so, therefore, what you -- in communities such as this, you are going to be drawing -- you are going to have a diminished scientific expertise on panels that require scientific representation if you require this.

Otherwise, I guess you are going to have to go outside of the community to do this. In this case it would be to another town in Alaska with a different population base, et cetera. So I could foresee this happening in different areas of this country where there are -- is a diminished pool of expertise in health care and in science, et cetera, in small communities.

PROFESSOR CHARO: Tom?

DR. MURRAY: I am not going to try to respond to Arturo. I think he has raised some very interesting and important perspectives. I think it can be dealt with. You can have a smaller board at a smaller institution. I assume the research would be lower volume. You could always call in a consultant to help explain it but I think we would need to -- we need to be mindful.

What I want to propose here in an effort to move us forward is an adaptation of what I think -- if I heard Alex right -- a suggestion he made, which is maybe to split this into the two recommendations or a two part recommendation. One being that a specific percentage, minimum percentage of membership of lay/noninstitutional members be part of the regulations.

So I put that up. And then secondly that that percentage be -- that minimum percentage be -- and then I would advocate 50 percent but I would not --

PROFESSOR CHARO: Would that be acceptable then for the next go around that there be a recommendation that a specific percentage of the membership of the IRB be made up of either lay people or unaffiliated people or both so that to some extent we will continue to -- we will allow a mixing and matching there?

And we might even want to say that ideally so that there is some room for exceptions to be made when needed because of special circumstances.

And that the second part of the recommendation would be to set that percentage at -- and then I have a feeling there will probably be a straw vote by e-mail before the next round of recommendations on what that number might be, whether it is 51 percent or 33 percent, or 25 percent or whatever.

Is that an acceptable way for the staff to move forward for the moment? Diane?

DR. SCOTT-JONES: One addition would be to retain the presence of the members at the meetings.

PROFESSOR CHARO: Sure. Sure. I was not intending to rewrite the recommendation in my summary.

PROFESSOR CAPRON: Excuse me, Alta.

PROFESSOR CHARO: Hang on just a moment, Alex. Trish, and then Alex.

PROFESSOR BACKLAR: And to make sure that one included in that membership people who would represent the populations who are being studied so those are -- that may change the membership. It would not be a permanent membership necessarily. You would bring people in according to -- you would not -- that would not eliminate bringing people in who would be representative of the populations being studied.

PROFESSOR CHARO: Are you suggesting that for every population or just for specific vulnerable groups?

PROFESSOR BACKLAR: For specific vulnerable groups.

PROFESSOR CHARO: Then we are going to get to that again so long as we can move the meeting forward because we are going to talk very specifically about what was not covered yesterday on vulnerable groups, so hold that thought for us, Trish. Thank you.

Alex, and then Diane.

PROFESSOR CAPRON: I would like us in the revised recommendation to separate out the consideration of noninstitutional members, unaffiliated members and laypersons because it does not seem to me that the conflict of interest

that is involved is the same in the two at all and institutional conflict of interest, that is to say the desire to approve research to accommodate a colleague, to further institution's financial interest and so forth exists for people, whatever their affiliation in the institution.

Whereas, the argument about having people who are not in the scientific field is people who will both ask the naive questions that get missed by the scientists but will also have independence of perspective in terms of why this research should be done or the attachment to it -- to a field of research, and that could be a person who is affiliated with the institution but is not a scientist working in the general area of biomedical research.

I do not see mixing the two of those because I do not really see the latter as a conflict of interest in the same way.

PROFESSOR CHARO: Diane?

DR. SCOTT-JONES: My question was exactly what Alex just spoke about and that is the distinction between lay members and nonaffiliated members. A lay member might be an affiliated person and so we need to think how we want the composition to be regarding lay and nonaffiliated.

PROFESSOR CHARO: Okay. Well, then that is very true. Many IRBs will use the chaplain at the hospital as a person who is affiliated but a lay person and you can imagine in this way also getting around the numerical problems.

Marjorie, I think you probably have enough now to try to redraft for further discussion and with your permission I am going to try to push on as it is now 20 to 11:00.

4.13 returns us to conflict of interest. This is also something that is obviously under great discussion within OHRP as we are all aware. Are there comments about the way this is now phrased or its basic thrust that need to be incorporated for the next draft since this will clearly be evolving in light of what happened in 4.12 and current events in Washington.

Bernie?

DR. LO: Two things. First, I think we need to say something about conflicts of interest for investigators as well as IRB members.

PROFESSOR CHARO: Okay.

DR. LO: And I think we should phrase it again to continue its planned activities to clarify, you know.

PROFESSOR CHARO: Other comments?

Diane?

DR. SCOTT-JONES: I have just a small question about this in relation to 4.12 because the last sentence of this recommendation, 4.13, says that institutions should develop policies to reduce potential institutional influence on their institutional review boards. 4.12 is exactly an effort to do just that and it seems that, if anything, these should be reversed in their order here so that they are logically more related to one another and I think also the last sentence needs

a little bit of work because of the word "institution" being repeated three times there.

PROFESSOR CHARO: Sure. Other comments?

Arturo, and then Alex?

DR. BRITO: I just have -- something I spoke to Marjorie independently in one of the breaks yesterday about and it is not a comment on the recommendation but about something the recommendation makes about conflict of -- this whole topic, conflicts of interest. I think in the educational component, I think that should be like the third component after you talk about regulations and the ethical standards, the ethical principles they are based on, I think one thing that investigators and IRBs need to be educated about is conflict of interest because I think sometimes those are unrecognized. So I just want to say that.

I know there have been some articles in the last few years. Donna Shalala had some really good literature on that and I can provide that for you but I think it is important, both of the financial conflict of interest and as an individual at an academic institution.

PROFESSOR CHARO: Alex?

PROFESSOR CAPRON: Two comments. One, I agree with Diane that the larger recommendation is institutional policies to avoid conflicts and that the subrecommendation is, in effect, one way of doing that is to have more noninstitutional members. So I think logically she is quite right. I do not have the problem that she does with the phrase "institution"

appearing a number of times in that sentence. It seems to me once is a noun and once is an adjective and once implicitly, and I think the word IRB is really not a problem linguistically.

I do hope that as we go forward with the point that Bernie raises about investigators' potential conflicts that we find a way of talking about the potentially even greater conflicts that nonaffiliated investigators, as we say those who are conducting contract investigations outside of institutions, face because in some ways we should see institutions not just as a problem but in many ways as a social mechanism for addressing the problem because institutions do have the ability to have good oversight mechanisms, good education and collegial influence towards better behavior.

And the implicit sort of nudging that happens when people are doing something and they talk with their colleagues and their colleagues say, "Well, you know, gee, that gives me some worry. Don't you think you should think about this or that," and without actually an investigation or a report or anything. The person adjusts behavior in a good direction. Whereas, the unaffiliated person, particularly if there are incentives built in for certain kinds of performance by the sponsor can be much more subject to influence and even almost, you know, I do not want to say "bribery" but I mean behavior that is not really scientifically valid and without the informal influences.

So let's not just run down institutions and see if there is a source of conflict but to also see the ways in which they can be helpful.

PROFESSOR CHARO: Bette?

MS. KRAMER: I think we ought to capture in one of the recommendations, I am not sure which one, the absolute requirement that every investigator needs to declare very much up front any interest, any equity interest, any interest that would accrue to his benefit that he has in the research in which he has proposed, the research he proposes to do.

PROFESSOR CHARO: Would that include, Bette, any fee that he is given per human participant enrolled in the research?

MS. KRAMER: I think so. I really do because, you know, if you were to exclude a fee -- I had not thought about this but if you were to exclude a fee then he could get around that where the fee instead of being a dollar per participant could be $100 per participant so that would be significant.

DR. LO: $10,000. They are actually --

MS. KRAMER: Oh, $10,000. Bernie likes the figure $10,000.

DR. LO: That is what it is.

PROFESSOR CAPRON: And then --

PROFESSOR CHARO: Alex, I am sorry, I am going to cut you off only because I am watching the clock and we have got a very big topic coming up next.

PROFESSOR CAPRON: Okay.

PROFESSOR CHARO: Okay. Marjorie, I am going to ask if under the circumstances you might be able to take this and go as far as you can with it in terms of notions of disclosure and the fundamental issue of conflict of interest, which is the ability to continue to work dispassionately.

MS. KRAMER:: That is the easiest way of getting at conflict of interest that I can think of.

PROFESSOR CHARO: And once again I think until we actually see another version of it, it is going to be hard to focus the discussion further down into the details.

Why don't -- I would like to see if we can go to the next recommendation because I think we need about half an hour for it.

Eric, is this --

DR. CASSELL: Next recommendation.

PROFESSOR CHARO: -- on the next recommendation? Okay. Try to take about 25 minutes to 30 minutes on it and then give Marjorie just a few minutes to talk about the as yet unwritten Chapter 5 which addresses the resource issue and in that way reserve ourselves at least a half an hour of time to discuss vulnerable populations.

Eric?

DR. CASSELL: Just one brief thing. As you rewrite a recommendation, if it showed up on e-mail individually rather than whole groups of them, just as you suggested before, they would be easier for us to focus on and comment on.

I just want to make a -- I think the idea of 4.14 is excellent but it should not be private organizations, it could be a public. It is organizations dedicated to the function should. You do not care whether they are private organizations that offer credentialing programs, do you? I mean, does it have to be private? Why couldn't it be P.S. 17?

PROFESSOR CHARO: Did you want to comment on that, Marjorie?

DR. SPEERS: I would only comment on it as far as I was -- what we were thinking about is not having it be the Federal Government.

DR. CASSELL: Well, then just make it organizations dedicated to the function should.

DR. SPEERS: Okay.

DR. CASSELL: Or independent organizations or something like that but private is not necessary.

PROFESSOR CAPRON: But you do not want to say independent because that sounds like it could be educational institutions that also do research. Do you mean that? No?

DR. SPEERS: No.

DR. CASSELL: Okay. Organizations dedicated to the function.

PROFESSOR CHARO: Other comments?

MS. KRAMER: Just a point of information.

PROFESSOR CHARO: Yes.

MS. KRAMER: Marjorie, why shouldn't it be the Federal Government?

DR. SPEERS: The general thinking in the field of credentialing or accreditation and certification is that the -- there is two points. One is that the members of that field, the professionals in that field, are the ones who are best able to identify best practices and set the standard for the field. So for most fields that is assumed to be individuals that are outside of the Federal Government, rather than in the Federal Government because most practice occurs outside of the Federal Government.

The second piece of it is that these organizations are viewed as being more credible when they have a certain amount of independence and when they have that independence from sponsors and from funders of the activities that are being undertaken.

MS. KRAMER: So would the Federal Government be contracting that out to an independent organization?

DR. SPEERS: No. They -- go ahead. Do you want to say something?

DR. MIIKE: I think the easiest way to look at it is that your husband is a specialist and he is certified by a subspecialty organization that is a private organization. It is not the Federal Government.

MS. KRAMER: I see.

PROFESSOR CHARO: Is this the place where we would incorporate Bernie's suggestion before that there might be an additional kind of credentialing that focuses on the ability to be the designated lead IRB for multicenter trials? It was a

suggestion that got a lot of heads nodding before. I would not want us to lose track of it.

DR. MIIKE: I am sorry.

PROFESSOR CHARO: Larry?

DR. MIIKE: I am sorry. Say that again.

PROFESSOR CHARO: Earlier Bernie had suggested during the conversation about multicenter trials that it might be that only IRBs that are particularly credentialed to be the lead IRB be permitted to become the so-called designated lead IRB when you have got a multicenter trial being reviewed only once by one group. In a sense the idea being that they -- there are separate skills that they need to have in order to be able to take over that role on the behalf of others. His analogy was remember the auto driver versus the bus driver and the truck driver.

DR. MIIKE: Yes. Can I respond before --

PROFESSOR CHARO: Please.

DR. MIIKE: I find that a difficult concept to accept. We are starting -- I thought that what we were heading for before that was that it would be more or less a mandate but then the institutions that do research among themselves would designate a lead IRB rather than some external body saying only this one can be the lead IRB if the institutions get together.

PROFESSOR CHARO: Just by way of clarification, as I understood it, it would simply be that they would all get together and decide among themselves which one it will be but they could not designate one that had not yet been shown to be

competent at that task so there might be two or three among them.

DR. MIIKE: I know but I still have difficulty with mixing up those two concepts.

PROFESSOR CHARO: Okay. Tom?

DR. MURRAY: Well, I always have respect for Larry's comments which leads me to wonder why I have a different reaction. My reaction is that certainly at this point in the stage of developing draft recommendations that this is an exceedingly creative idea and that I take it what it is an effort to respond to is the sense that more will be at stake if one IRB is approving a multicenter trial and that there will be some IRBs that may function quite well at a local institutional level but might be simply of insufficient sophistication or means to deal with this greater trust and that so a parallel -- you know, they could be accredited for -- an IRB could be accredited to be an IRB for local review but it would have to meet a higher standard to be also accredited to become an IRB capable of reviewing these multicenter trials.

I think that is a promising notion and I am wondering what Larry's reservations are about that.

DR. MIIKE: Well, I am thinking one of two issues. One of timeliness in implementing these recommendations because if we are talking about waiting until that happens you have got to go through the whole credentialing process for IRBs and then on top of that another layer for what might be a subspecialty IRB.

The other one would be the whole issue of voluntariness of multiple institutions to reach their own accommodation and I would doubt that multicenter institutions would pick the one that is least capable of being the designated IRB.

DR. MURRAY: I am not -- I guess I do not see the -- I do not see a problem with the latter. First of all, this is accrediting and credentialing. It is already in motion. I mean, this is not -- this will not be a new idea from us. It is basically us blessing something for which there already is considerable momentum. So realistically by the time we are -- our recommendations even become accepted it is going to be even further along and maybe it will already be fully --

DR. MIIKE: But not in the multi-step that we are --

DR. MURRAY: Right. We are suggesting a new wrinkle if we go with this recommendation. And my guess is in most cases it is going to be the principal investigator's institution that will be the one -- his IRB will be the one we turn to first. That is probably going not happen in an overwhelming majority of cases and if I am wrong about that empirical claim I would like to be told and the chances are it is likely to be a fairly large and sophisticated institution with a large and capable IRB. So I do not think there will be a lot of -- I do not anticipate a lot of vying to be the IRB in charge here but I could be wrong about that.

PROFESSOR CHARO: Bernie?

DR. LO: I just wonder if one way out of this is to soften the language and say that the central office consider the feasibility and desirability of incorporating into the assurance process whatever we are talking about, accreditation process, a provision by which IRBs may seek accreditation so to make it -- we are going to think about and consider rather than they should do it. I mean, I think it is really an idea to flow rather than saying it has to be done.

But let me say something else about Recommendation 4.14 and 4.15. I agree with Tom that this is already happening and it is going to happen. It is not really our idea. But I think there is sort of a fundamental recommendation that is sort of the assumption behind 4.14 and 4.15, which is that researchers and IRBs ought to have demonstrated their understanding of research ethics and the pertinent federal regulations and accreditation and certification are a means to demonstrate that so that I think it is the -- you know, demonstrating the proficiency is sort of a fundamental recommendation and then the accreditation and certification of the means to accomplish that otherwise it is, you know, why are we accrediting. It is because we want to make sure people are capable of doing what they are supposed to be doing.

PROFESSOR CHARO: Bette, did you --

MS. KRAMER: No.

PROFESSOR CHARO: I would like to ask a clarifying question if I may from everybody here as well as from Marjorie and that has to do with the -- what is anticipated in terms of

multiple credentialing organizations. I am not aware of whether there is only one or if there are going to be competing -- the recommendation as written seems to anticipate the possibility of multiple credential organizations and says basically that the government could choose to recognize the credentials, the accreditation of any organization that ensures that their program -- ensures that there is competency in the basic federal regulations, right, but I want to make sure I understood the intent here.

I also wanted to ask about anybody's expectation of kind of specialty accreditation. In certain areas of research that are extremely controversial, and I am thinking specifically about embryo research and fetal research as well as research that involves women who are childbearing potential, even research with the cognitively impaired, et cetera, that there is the possibility of specialty credentialing, which there are IRBs that are now pledged to follow certain kinds of practices that are consist with the federal rules but then perhaps, for example, do not permit certain research that would be permitted under the federal rules but at this institution are not permitted and there is a stamp that identifies the institution as such.

I just would like to know how much this kind of multiple accrediting and kind of branding have been anticipated and how we expect this will all work.

DR. SPEERS: I think you ask two questions. I think the first one was did we anticipate there being multiple

accrediting bodies and the answer is, yes, we did anticipate that. That is the reality now that there are several. We did think about whether the -- whether it would be appropriate for the Federal Government in terms of the central office to select one over another and decided that it probably would not be appropriate to do that but instead if all of the accrediting bodies meet standards then being accredited by any of them should fulfill the government requirements.

What -- I am going to answer your second part but I do want to focus you on recommendation 4.14, the last sentence, which says that federal agencies should require institutions to become accredited. You know, I think you do need to make some statement about whether accreditation should be mandatory or voluntary. So I think that that does require some conversation.

In terms of levels of accreditation, what we have thought about that is not in this draft is if you move to a notion of central IRBs or at least to a recommendation that an institution does not have to have its own IRB then an institution could be accredited to conduct research. That is one level of accreditation.

A second level is to conduct an review so that you deal with institutions that have IRBs and institutions that do not have IRBs, as well as IRBs, the independent IRBs that exist. So we have thought some about that and that could be discussed in here.

We have not specifically thought about the issue you raise of whether an IRB conducts some kind of special research, whether it should have some type of special accreditation. The way that that is dealt with in the report now is when we talk about very risky research, research involving unknown risks or very controversial research, that there is a need for some additional review that could be handled through a national panel or some other type of review body. So we dealt with that outside of the accreditation issue in a sense in this report but another way to deal with it could be through accreditation.

PROFESSOR CHARO: Larry and Bernie?

DR. MIIKE: Yes. I know it is real late to introduce this concept but just looking at these recommendations I think you can deal with the side that does the review of ethical conduct and the validity of the research, which is the IRB side, and then the people who conduct the research, the investigators, and we are asking for certification on ethical issues on both, I think we are going to run into trouble when people look at that and they will say, oh, it makes sense in the IRB side but the investigator side -- now we have got to go through a certification process.

And I wonder whether we might have another alternative which is the usual way of dealing with these things, which is continuing education requirements where rather than having to be certified that is a part of -- it is an easier requirement to go to a course or a conference with a focus on ethical issues.

I know it is late to bring it in but it just occurred to me that we are going to run into trouble when we deal with both sides of that.

PROFESSOR CHARO: Bernie and Eric?

DR. LO: Yes, a couple of points. I mean, I think it is good to think separately about institutions, IRBs and investigators. Let me just say under IRBs, I think we omitted IRB members, and it seems to me they need to get certified as well as chairs and administrators in the last sentence of 4.14.

Larry makes a good point about investigators. I mean, there is currently a requirement that in order to submit a PHS grant you have to be certified by your institution and, as Larry suggests, it is often you have taken basically a CME course on research ethics. So it is not a national body that certifies you but your local institution that certifies you. So who does the certification may be different for the investigators than for the institutions or the IRB members.

And actually I think Greg Koski's plan envisages more than national voluntary certification program would be more for the IRBs, not for the investigators. So I agree with Larry on that one.

I think Alta raises an interesting point which I would just again not try and settle and just say here is the issue I want people to think about and that is the issue in depth or subspecialty certification. I actually like for -- as you know, I have been very concerned about having a central IRB have to review particularly controversial research and the

other option is to say if you want to engage in research on people with impaired capacity or embryo research, your IRB has to have special certification to make sure we really -- you have demonstrated you really thought through these issues in depth.

And, in fact, it would make sense for that to be a much tighter certification than sort of a general certification. I actually think it is something we should throw out for people to think about and it is more sort of a good idea and someone else needs to pursue it rather than our trying to work out the details.

PROFESSOR CHARO: Eric?

DR. CASSELL: Well, Larry, I agree that there is no question that certification will create a bureaucracy and all of that but on the other hand it will also educate people who should be. All of us who do CME have already been certified. So there may be an ongoing component of education but there should be a primary certification.

PROFESSOR CHARO: I would like to interject something also on the point about the investigators. Ordinarily I have always thought about the accreditation certification process as one that involves a quid pro quo. It is not just an add on to the current system. The accreditation's quid pro quo is the elimination of the annual negotiation over the MPA, which was as documented in the text beginning to devolve into a purely bureaucratic exercise.

When you look at the investigators you have got to ask what is the quid pro quo for all of this, especially now again as we expand into the currently uncovered areas of the private sector. Is the goal here to make it impossible for anybody to embark on doing human subjects research until they have passed some kind of licensing test even though we have also set up some oversight through the IRB system that they have to go through where the IRBs are now credentialed and accredited and serve as an oversight.

Or is it that certification for investigators is something that is not mandatory prior to doing research but it is desirable if you want to cash in on some of the quid pro quos. One of the might be eligibility for PHS funding. Another might have to do with the way in which your paperwork flows to make it easier for you.

I mean, as a basic question I am not sure I have yet heard the case made out for mandatory certification of investigators prior to them being permitted to do human subjects research versus making certification or CME, either one, or at least, you know, continuing ed, CE, something that is desirable because they get something in exchange and everybody benefits.

PROFESSOR CAPRON: Hand up.

PROFESSOR CHARO: Okay. Trish, Bernie, Bill and Alex.

PROFESSOR BACKLAR: I would like to explore the fact that other professionals have certain tests that they have to pass. Lawyers have to pass a bar exam in their states and as

Alta told me during our discussion in the break that apparently they also can pass a national test. Some kind of test that is more than just the bar exam.

PROFESSOR CHARO: No, I do not think that is a conversation I recall.

PROFESSOR BACKLAR: All right. Well -- but the other thing is that if they want to practice in another state they have to pass the bar exam in that state and so if researchers are going to do research it seems to me that it might be wise to have a national test.

PROFESSOR CHARO: Bernie?

DR. LO: Yes, Alta, in response to your question I think the quid pro quo is you get to carry out research on human beings that you otherwise do not have a right to do.

PROFESSOR BACKLAR: Right.

PROFESSOR CHARO: So, Bernie, just to clarify, so a graduate student who wants to do survey research is going to have to get certified before being able to.

DR. LO: Well, certified in the sense they need to go through some course work or a seminar or --

PROFESSOR CHARO: Okay.

DR. LO: -- you know, something.

PROFESSOR CHARO: I just want to make sure I understand completely how this would operate.

DR. LO: Certification can be folded in with the rest of your education but it is just before we let you do this you have to demonstrate you are capable of doing it.

PROFESSOR CHARO: Bill and then Alex.

MR. OLDAKER: I will say something a little heretical. I think that -- I think the certification is important. It is somewhat important on the educational basis but if we have different certifying boards we are going to have differentiations in probably the level of understanding that various people go through.

But I think the important point of certification is the ability for whatever we call this national organization along with the certifying boards to have the ability to decertify. Decertification is probably the strongest type of punitive action that you can take easily to remedy problems without it being an over arching cutting off of a university or something else.

So I think that just the fact that they are certified and can be decertified and a decertification is likely -- the security is you learn someone else is losing their ability to do what they want to do is a fairly important and fairly punitive action. And I think that -- I have not read it here but I think the central body should have that ability to both decertify researchers and decertify IRBs.

PROFESSOR CHARO: Alex?

PROFESSOR CAPRON: A couple of comments. I may have misunderstood you, Alta, but to the extent that you were disagreeing with Bernie on the issue of certifying investigators, I agree with the point he made that there is already a requirement that investigators be certified. The

only question that would then be raised in terms of a quid pro quo is, is there some reason for thinking that that is an unacceptable requirement or something, which I do not think there is any reason for thinking so. So I do not think that we have to do the quid pro quo argument vis-a-vis investigators.

I do believe that the separation that Marjorie suggests between institutions as research institutions and as review institutions is appropriate and it seems to me that a part of the research institution accreditation would be the ability to examine its own investigators and determine their competence to become investigators. And as most people say, this is a form of a CME with an examination, often a web-based examination that institutions are now applying. And what would happen would be part of the accreditation process would be asking is the institution doing that in a reasonable fashion, are they requiring enough education, are they giving a good exam.

The final point is in response to Marjorie's description on how accreditation fits in with the Federal Government. What we are basically thinking about as far as I can tell is something that is usually referred to as deemed status where an institution by being accredited by an organization that is recognized as a valid accreditor is deemed to have met the federal requirements.

But in that model, Marjorie, the underlying idea is that there is usually some alternative governmentally based way of getting approved and the reason for going for accreditation

is that it is seen as more pertinent, more peer-based and less bureaucratic, et cetera, et cetera. But the institution always has the other alternative and I think we do need to address whether that is what we have in mind or if we are saying that the only way to get approved would be through a private -- that is to say nongovernmental -- it could be a public institution in the sense of a state sponsored --

PROFESSOR CHARO: Larry?

DR. MIIKE: Well, Bernie had mentioned in one of the statements that he thought that IRB members also should be certified. I think there needs to be a distinction between the administrators and the chairs and the members just as there should be a distinction between the principle investigator and other researchers in the field such as your graduate student. So I think we need more rigorous requirements on the leaders in these areas subject to certification and then perhaps something softer like the continuing education requirements for the others because, you know, they are going to turn over a lot in the IRBs and in research.

PROFESSOR CHARO: I am going to put myself on the list just because I do think that there is still a lingering problem out here and it may be that I am alone in my concern about this and I am certainly persuadable but there are a tremendous number of places currently that do not have MPAs, typically liberal arts colleges, for example, where people do engage in research and it is not funded by the Federal Government. Frequently it is not even funded by their departments. It is

just what they are doing. And this would be very common in the social sciences and even in some areas of the humanities.

And because we are proposing to extend the human subjects protection system with the entire panoply of federal regulation to all of that research because it involves human subjects and make all of that research now subject to IRB review by what is now going to be accredited IRBs with certified administrators and certified chairs and certified worker who are educated members, we have instituted a fair amount of control over previously unregulated research.

Then the question arises do we also need to add yet another level of protection, which is to make sure that each of these individuals is either certified or has been exposed to some minimal amount of education?

I think this is going to be a larger number of people than we are anticipating. I disagree with Alex about the fact that there is already this quid pro -- that there is already a requirement. What there is now is a carrot which is eligibility for certain kinds of funding or if you are in certain kinds of institutions the privilege to continue with that institution but there are many people for whom this is not a requirement. It is a brand new requirement on top of the IRB review.

And I want to make sure that we are really convinced that it is necessary in light of the other protections that will be provided by the IRBs that they are now going to have to

go through. Especially where research is undertaken sporadically by these individuals.

I fear that this is going to be seen as a major obstacle to what is frequently minimal risk and is often of very great importance to them individually because it furthers their own research agenda but it is not part of a kind of massive research agenda that, you know, nationally where they are an important cog in the wheel. I mean, I just want to make sure that this is not overkill. That is all. I am persuadable but I want to make sure it is not overkill.

PROFESSOR CAPRON: Doesn't the sporadic nature of their involvement almost argue the other way that these are people who would be in greatest need of being familiar with the standards?

PROFESSOR CHARO: I agree that they are the least likely to know what the standards are but so long as they have to go through IRBs they are going to be disciplined by the IRBs. Now they may be unhappy when they discover what those standards are that they never thought of before but it is not as if they are going to be totally unchecked. The question is whether the IRBs can be a sufficient check or if they need the prior education as well.

Bernie?

DR. LO: Alta, I guess I just find it hard to be sympathetic to the idea that you can spend one day of your life going to a course on research ethics. That is really all it is

even for, you know, a lot of high powered research institutions and I think that may be all it takes.

PROFESSOR CHARO: Okay.

DR. LO: The fact these people are doing minimal risk research means that they often will be either exempted or get what we are calling administrative review and so they may get very cursory oversight from their IRB. In fact, we are hoping to lighten the scrutiny requirements.

I do not think this is asking too much as long as you do not have to sort of do a national standardized test and send $50 and stuff. I mean, just go to a course in your city for half a day and, you know, get the little piece of paper.

PROFESSOR CHARO: All right. It is -- I can see this is not going -- I always imagine that the certification might exempt you from some of the more onerous forms of monitoring and continuing review whereas without certification you would be subject to it to create that kind of control but I can see this is not going to be something that sways most people.

We are at 11:15. Are there any other urgent comments about the accreditation and certification process to give the staff some direction because, if not, I wanted to move on briefly to Chapter 5? I want to give people an opportunity for last licks at 4.14 and 4.15.

DR. MIIKE: Are we going to say anything about the last recommended?

PROFESSOR CHARO: Oh, I am sorry. We do have 4.16 to go through. I am sorry. But still last licks at 4.14 and 4.15. Okay. 4.16?

DR. CASSELL: Could I know why -- what the function of this recommendation is, Marjorie?

DR. SPEERS: The function of it is, in part, to -- there is two pieces to it. One is that the FDA conducts inspections and those inspections -- they seem to function -- they seem to focus on both data, the data, the quality of the data and somewhat on IRBs and IRB review.

These inspections are conducted after the research is completed and what we are suggesting is that FDA inspections should not concentrate on IRB review and be used as a way of monitoring human participant protection but instead should focus on the quality of the data and the IRB reviews should be dealt with in other ways.

DR. CASSELL: Couldn't -- I mean, if you are telling another agency that has a long track record what to do, couldn't it be turned around somewhat to suggest that in light of the previous recommendations the FDA may no longer have to. The job will be better done another way. Otherwise you are telling the FDA what to do and I do not think they listen too well.

PROFESSOR CAPRON: Hand up.

DR. MESLIN: Okay, Alex. You are after Tom and Diane. Tom?

PROFESSOR CAPRON: Okay.

DR. MURRAY: I may misunderstand some of the FDA practices but I believe that as a matter of fact the FDA does, indeed, do some in process monitoring of human trials and further, in fact, that just about the only monitoring of trials in process is done by the FDA right now. So we could find ourselves in the very ironic position if we adopted this recommendation that this is the only one that is actually implemented and it removes the only source of actual monitoring that happens in the U.S. today. So that, I think, would be a very unfortunate result.

DR. MESLIN: Diane?

DR. SCOTT-JONES: I was just wondering whether this would be usefully moved to join the other earlier recommendations on monitoring. It seems to stick out just a little bit here and I was not quite clear in reading through the text why it belongs here at the end as opposed to in the earlier sections. I think it would be clearer.

DR. SPEERS: There is also another potential way to deal with this and that is we are recommending that there would be one set of regulations. What that implies is that the FDA regulations would become part of this one set of regulation and these site inspections then would be dealt with when a set of regulations is written so it may not require a separate recommendation. It could be dealt with in the text.

DR. MESLIN: Alex?

PROFESSOR CAPRON: I think Diane's suggestion is a good one. I think we are mixing, Marjorie, a little bit of

apples and oranges here. The monitoring of data is a valuable function. It does mostly now occur in FDA related investigations which are leading up to the approval of a drug. There may be other instances in which it is advisable but it seems to me it is separate from the institutional accreditation issue.

Since we are assuming the institutional accreditation for all site visits by appropriate people to the institution, if there is a quid pro quo of the type Alta was talking about, this -- it could be discussed -- the FDA aspect could be discussed in the material under 4.14 by leading up to it or after it. However, I guess we are now just doing -- leading up to it.

That is to say institutions would face -- if the FDA can sign on to this and use accreditation as meaning that you are doing the job you should vis-a-vis the drugs that go through your institution for testing. The FDA investigations might be lessons that the FDA might actually be able to coordinate its efforts with this accreditation process. That is what HHS does now with the Joint Commission's accreditation process for hospitals where they do a spot monitoring or spot checking of the accreditation rather than trying to inspect all the hospitals themselves.

DR. MESLIN: Bernie?

DR. LO: I guess I am in favor of some of the things the FDA now does. They are the only group that actually looks to see whether there was a consent form as a proxy for informed

consent and they have found that in some cases people did not know they were in research.

PROFESSOR CAPRON: But the accreditors should be doing that, Bernie?

DR. LO: Well, but the accreditors are not going to do it. Alex, I would disagree. What the accreditation proves is that you have the knowledge and the structure in place. I do not think the accreditation is going to get to individual studies going and pulling charts. Now it may or it may not.

PROFESSOR CAPRON: It could. I mean, today, Bernie, sorry to interrupt but today accreditation is increasingly moving to outcome measures, not just standards. I think that is important and very necessary in the case of hospitals and there is every reason why the performance should be measured, not just the structural ability to perform. I quite agree with you. If that were all that happened it would not be adequate. But it would be much better to encourage a good accreditation process which really looks at what the institution does rather than having a duplication of the FDA.

The monitoring function for things that need a Data Safety Monitoring Board and the like to be set up and the FDA makes sure that that is happening, that is a separate issue and it is not true of every research project, although, as I say, it probably should be true beyond just certain drug trials.

DR. LO: Well, maybe then what we are trying to say here is that we should avoid duplication in oversight, that the FDA, the accrediting bodies and all the other people ought to

divvy up who looks at what, and if somebody is taking care to make sure the investigators and the institutions are always doing their job, the other people ought to say we will take your word for it as opposed to -- so it is a -- I think so that if this is phrased if the accreditation evolves to the point where it is outcomes based rather than just process based then the FDA should consider shifting the focus so it no longer duplicates what the accrediting body may do or something like that.

PROFESSOR CAPON: That sounds good to me.

DR. MIIKE: I just want to add on the accreditation side that it may be true that they are moving toward outcomes but it is not the accrediting body that goes in and looks. I mean, they set the standards for which an institution should be establishing a monitoring outcome program. So it is not quite the same as the FDA going in and being an outside body coming in.

PROFESSOR CAPRON: That is not actually correct. The accrediting bodies send in the surveyors. They have a dual function of setting the standards which have to meet federal requirements.

DR. MIIKE: Okay. You are talking mostly about joint commission. I am talking more about the quality assurance. The measures that the HMOs and others are doing.

PROFESSOR CAPRON: That is true. I mean, they are not -- they do not go through the same process, I agree. It would be very interesting to me to see whether NCQA can do the job

that the VA has contracted with it for because their process is not like the joint commission's process.

DISCUSSION: CHAPTER 5

PROFESSOR CHARO: Other comments? Okay. Why don't we move on then to Chapter 5 very briefly because it is not before us but I would like to ask Marjorie first just to give us an idea of what she expects to be in that chapter and then take a few moments for essential feedback while it first gets drafted.

DR. SPEERS: Chapter 5 is still an outline in my head as much as anything but as I mentioned to you yesterday we really want to try to do two things in Chapter 5. One of the things that we want to do is to come back now that readers will have Chapters 2, 3 and 4 in front of them and to point out the connections in the system, to -- just as we were discussing now issues around, for example, accrediting and certification if we go back and look at the education recommendations. If some of those were implemented then they make certification of investigators easier because education is occurring perhaps as part of graduate training or medical training. So to point out those kinds of interconnections in the system.

We also want to discuss in that part the need for resources and the need to properly resource the oversight system, not just the IRBs or the institution but the entire oversight system. And we will need to, when we talk about resources, talk about -- somewhat about who is responsible for providing the resources and ways that those resources can provide the mechanisms for providing resources. And I suspect

that will be as important if not more important than trying to actually cost out this -- the cost of this program because I am not sure we can do that.

We also want in Chapter 5 to look at this report in relation to all of the other reports that you have produced and to talk about, for example, ways that the commission has evolved over time in its thinking. I think that is important for us to do as much as we can do that reflecting upon ourselves to talk about if there are any -- clearly talk about the consistencies and if there are any inconsistencies among the reports with this one, between the other reports and this one that we discuss those as well.

I say this every time with every chapter we have written, I do not think this chapter is going to be very long and then you end up with 50 pages. I do not think this chapter is going to be as long so I am not -- this is not to completely rewrite the report in the final chapter but it is to point out some of the linkages that may not be obvious to individuals.

We have had some ideas. I think some good suggestions that were made here, for example. One of them was to have a summary of where we have reduced burdens on IRBs and that is the kind of thing that could go into Chapter 5 to point out differences between the current system and what has been recommended here. Some of those kinds of summaries are what we envision to go in Chapter 5.

PROFESSOR CHARO: Bette and then Larry.

MS. KRAMER: What are we going to say about funding? Who is going to get funded? How are they going to be funded?

PROFESSOR CHARO: What would you like to say about funding, Bette?

MS. KRAMER: What I would like to say about funding is that all of this needs to be funded. Now who should fund it or who should -- which groups or which participants should participate in the funding, how it should be divided up among them, I do not know. But for sure it needs to get funded.

PROFESSOR CHARO: Larry?

DR. MIIKE: From what I hear, and I support it wholeheartedly, is that this is not going to be a usual summary chapter where we just sort of take the recommendation and say here it is. So it is really important. I think this is probably what should be published as a separate summary of our report so everyone can read it.

And I think the emphasis should be that we are redesigning the whole system and that -- and especially the trade offs where -- and we have got to say up front what we talked about yesterday where we are broadening the potential area which we are going to cover but we understand the practicalities of what we need to do and even though we cannot say with precision how we are going to reduce the scope once we make this broad definition that the intent is that once we begin to implement the system we start to gain knowledge about which areas we can pay less attention to and which areas we have to focus on.

So I think it is really important to set that tone that we are not just sort of increasing the regulatory burden and building this huge bureaucracy and that we are really trying to focus on the areas in which the participants in research need the greatest protection.

PROFESSOR CHARO: Other comments? Bette?

MS. KRAMER: Yes. I would like, if possible, for us to tie back into our earlier reports and point out why all this became necessary as we have gone through the past few years and again with --

(Simultaneous discussion.)

MS. KRAMER: Pardon?

DR. CASSELL: I am just saying --

MS. KRAMER: Oh. And again with relationship to the funding, how we were restricted in what we could require of different participants, or when I say participants, participating groups or organizations as we did these other reports because the funding just was not there. So that this is something that has become necessary as -- the importance of this has become more and more necessary as we have gone through each succeeding report that it has become apparent to us that this is an absolute requirement these changes be made.

PROFESSOR CHARO: Larry?

DR. MIIKE: I have to disagree with that. I do not want us to sort of be on the defensive and apologize for things that we were not able to do and I would rather -- if you are going to keep a chart I would rather not rehash all our old

reports and how they might fit in this. I think we should stay focused on reforming the fundamental oversight system and that is what we should be focusing on. It cannot be -- we cannot cover too much ground on this last chapter. Otherwise it is going to get long and it is going to get diffuse in its effect.

PROFESSOR CHARO: Eric Meslin?

DR. MESLIN: Just very quickly on that last point, Larry, I think the idea in looking back at previous reports is not to simply compile the executive summaries and say this is what we said. The idea would rather be to look horizontally across reports and identify the several consistent themes that have come out about informed consent, about assessment of risk that show that this particular report, while different in both structure and function as compared to other reports, is also the -- is also mindful of what the commission has said before.

And there are places in the current oversight report, and you have already identified a couple of them, you know, identifiability with -- for example, where it will be useful for the readership of this report to be made aware that the commission's thinking has either been informed over the last couple of years. It itself has been informed.

So I quite agree that the idea of that last chapter is not simply (a) apologize for what we could not do and this is the time when we are going to do it or (b) simply compile again all 52 of the recommendations or 65 if you add in the international report's recommendations and duplicate them but

rather to look more thematically, if anything, and to show how this is a logical conclusion.

PROFESSOR CHARO: Bernie and Arturo, and then I am going to try to cut it off so we can have some time to discuss vulnerable populations.

DR. LO: I would like to suggest that we shift the focus from NBAC to the stakeholders of research who are going to be impacted by the report so what I would like to suggest we do is go through and identify the people who are going to be affected by this report, investigators, IRBs, institutions, sponsors, and try briefly to say to them this is how it is going to change for you if this comes to pass, this is why we think it is a good idea.

I think that the people reading this are going to -- well, they are going to care less about how we got here than what it is going to mean for them and I think they need to get some help in trying to understand why it is in their interest to support the kinds of recommendations we are making and what is going to happen to them under these new proposals.

PROFESSOR CHARO: Arturo?

DR. BRITO: Before Bernie's comment it was almost like I was getting a sense of finality here and I understand the reasons for that but I think that the tone here has to be that this is a dynamic process and even though we are making big recommendations -- changes for big -- recommendations for big changes, it is still a dynamic process and what we have learned over the past few years as a commission and how that applies to

this currently and what we can expect in the future and what we do not know what to expect in the future and the reason for future bodies to deliberate on this and, you know, the continuing need for deliberations.

So there needs to be not a tone of finality or this is it and this is the big change and this is it but a tone of the dynamic process.

PROFESSOR CHARO: Okay. Diane, do you want the last word?

DR. SCOTT-JONES: I just wanted to say one small thing. It does not have to be the last word. I wanted to say that -- along the lines of what Arturo said and Bernie. I really like the idea of having in the last chapter something strong about both an ongoing process and about stakeholders. I like very much the tone of inclusiveness in the report, of not focusing simply on the needs of researchers or the needs of institutions but on the needs of the American people, and I think that is just a great part of this report, the tone of inclusiveness, and I would like to see that.

DR. CASSELL: That is a pretty good last word, isn't it?

(Laughter.)

DISCUSSION: VULNERABLE POPULATIONS

PROFESSOR CHARO: Okay. Thank you.

With that, I would like to turn our attention for the last 24 minutes to a topic we visited yesterday and, Alex, with apologies, you are going to be somewhat at a disadvantage here

because you were not able to hear what happened but let me tell you that most of what you have seen so far has been substantially changed and so you may be a little bit misled by the language that you were able to review up until now.

PROFESSOR CAPRON: Okay.

PROFESSOR CHARO: In recommendations 3.11 and 3.12 yesterday we talked for some time about how we would like vulnerability to be described in the future and there was some consensus that it makes sense to think about vulnerability in terms of the individual aspects of the relationship between participant and investigator that creates a vulnerability in the context of that particular protocol rather than thinking solely in terms of the intrinsic qualities of the person, whether a child or somebody who is cognitively impaired or somebody who is in prison, et cetera.

What we did not decide in 3.11 was whether we wanted this new way of kind of deconstructing vulnerability into all of its various components to completely supplant the current system, which includes subparts that identify specific groups that have one or more of these characteristics and then attaches very specific rules that should be applied when research is reviewed that concerns that.

If we wanted to completely supplant that system or simply supplement it in the sense that this new approach to vulnerability would be used so that IRBs who are looking at participants who are not specifically covered on that list of vulnerable groups might nonetheless be identified as having a

particular vulnerability in that research protocol which should be addressed. And that is one thing that was not completely clarified and would help the staff a lot.

The second has to do with 3.12 and it involves something toward the end of 3.12, and that is as follows:

There is a suggestion that with the exception of those who have difficulty giving consent for themselves that people who are somewhat vulnerable in the context of a particular proposed area of research should nonetheless be freely used in research, that we should not be avoiding the opportunity to do research on those populations and we think implicitly the reason is that we want to learn about those people and make sure that the results of the research are applicable to them.

On the other hand, in the subparts that currently exist with regard to vulnerable populations a consistent theme has been that you do not use these populations unless the research could not sensibly be carried out on alternative populations that are not vulnerable. There is some conflict here and we would hope to resolve it in order to give direction.

So I would like to suggest that we spend the last 25 minutes on those two questions. The first about the interplay between a general notion of vulnerability and specific subparts or specific identified populations and, second, about the way in which we approach their inclusion in research as a general matter or as only a special matter.

Okay. Comments?

Diane?

DR. SCOTT-JONES: I will start trying to answer some of the questions you have posed. I cannot remember all of them, Alta, but you asked whether this way -- this analytical approach that we have proposed in the text that very nicely lays out dimensions along which a person might be vulnerable should add to or supplant the previous way or the present way of identifying groups of persons.

PROFESSOR CHARO: Correct.

DR. SCOTT-JONES: It seems that it would be most useful if this in some way adds to that way of using groups.

The problem that arises when you use groups like that is that they are used in a rather rigid way and in a way that might not be the most useful so it seems that there would be many instances in which you would need to refer to groups and not just the dimensions. So it seems that they used somehow together and I do not know how specific we need to be about that.

I am trying to think. What were your other questions, Alta? I cannot remember all of them.

PROFESSOR CHARO: Well, why don't we just stop there for the moment and focus on that one first.

DR. SCOTT-JONES: Okay.

PROFESSOR CHARO: And get a sense of the commission. I do not know that we need to be completely specific so much as clarify for the staff what direction they want us to go.

Other reactions? Larry?

DR. MIIKE: The question that we needed to answer is how well has the current groupings worked and if they have worked to protect fairly well children and the others then it does not make any sense to get rid of it simply because we have come up with a better analytical approach.

One could say that we could supplement that by using those -- in those particular categories using that as the initial guidelines but then using the analytical approach to refine any kind of the protections around that but I think we should also make a statement that we do not endorse any more additional grouping such as the way it is now but that -- but any future possible groupings of vulnerable populations be addressed.

PROFESSOR CHARO: Of course, in the capacity report we did suggest an additional grouping.

At the time we were working within the context of current regulations and thinking about something that fit comfortably within the current scheme. Would you want the recommendations in that report to be kind of reviewed and reanalyzed in light of a more general notion of vulnerability or would you want to make that another group that would be pulled out for special attention?

DR. MIIKE: Well, I guess that would depend on the analysis that is anticipated in Chapter 5 about the compatibilities and inconsistencies between our past reports and our over arching. That is a punt.

(Laughter.)

PROFESSOR CHARO: Other comments?

If we follow Diane's approach, which is supplementary, the way it might look would be that there could be groups that are identified as being typically vulnerable across most kinds of protocols. It would allow for special rules to be written for those groups that would be carefully tailored to them. Groups that are not mentioned. People that are not mentioned specifically would nonetheless be eligible for particular attention because IRBs would be directed to look for other forms of vulnerability that had not been previously identified.

So a study that involves institutionalized persons other than prisoners might suddenly raise a red flag for the IRB and they would ask whether or not there is a vulnerability here that needs special attention but they would not have been singled out systematically for special attention across all protocols. That is how Diane's suggestion would work.

Bernie?

DR. LO: Let me try and articulate a simplistic way of looking at this. The basic issue we want to get across is that vulnerable populations in research need special protection and (a) we would like to see some review of how the current scheme of singling out certain groups to have specific recommendations actually works in context. I mean, I agree with Larry. I do not think we really know and I do not think it has been systematically studied whether the current group approach with a separate set of subpart regulations carries out that task of

protecting subjects who are -- participants who are identified as vulnerable.

And I think the subpart B is that in addition to those groups that traditionally have been considered as being vulnerable, we think there are other groups that merit -- other individuals in a study that merit additional protection. As, for example, through the analytic scheme that is presented in the text and the paper.

And I think Diane's point about supplementation is that as an IRB or investigator, I should not just say, well, I am not dealing with, you know, women, children, da, da, da, prisoners, so I do not have to worry about it. I have to go through a more kind of nuanced analysis of whether some of my participants are vulnerable in ways that were not obvious from that kind of approach and then to also have a tool kit of potential responses to either reduce their vulnerability or to ensure that they are adequately protected.

So I guess I am a little concerned about our making sweeping judgment whether we should either supplement or refine because to me the unanswered question is how well is the current system working to achieve the purposes that we are all in agreement with.

I think if we sort of keep that attitude that don't we all want to protect people who are vulnerable but we have to make sure we can identify them and whatever regulations are proposed actually do that task without onerous side effects.

PROFESSOR CHARO: Eric Meslin?

DR. MESLIN: Bernie, my hearing of what I think was the consensus was slightly different from your first sentence and it was there is agreement that individuals who are vulnerable in particular ways deserve protection. You had referred to populations and I think that the conceptual shift that is trying to be made here was the one that Diane was describing.

But as a point of, I think, reminder about the capacity report, what you all said was not that there must be a subpart E but that there are a number of ways in which the additional protections that this population of individuals could be provided includes -- perhaps including a subpart E, it left open -- subpart E, it left open the possibility that adding to the alphabet of vulnerable populations would be this one and we heard a great many critiques and comments about making that type of choice.

This orientation has a pretty clear suggestion, which is the line that says requirements concerning vulnerable populations should be incorporated into one uniform set of regulation. It may be that what you want to do as a group is to take the capacity report's approach and simply say the kind of categorical vulnerability which we all agree is important and worth highlighting should be given greater emphasis and that there are a number of ways to do that.

But the -- using Larry's worry, one of the ways that the commission does not want to go is to simply add a list of alphabetical populations to that list. One option is to

combine all of them under one regulation. Another is to -- I am trying to find a way to say what you are saying but make sure that it is -- the options are clear to you because the staff discussion was certainly at the level of putting all of this under one tent and focusing on the analytic method of highlighting vulnerability rather than as we now know from our federal survey there are some agencies that do adopt certain subparts and some that do not. And that does not seem to be -- does not seem to be useful.

PROFESSOR CHARO: Marjorie?

DR. SPEERS: Let me -- having worked with the three subparts and having some idea of how they work, the argument that I could envision writing -- the easiest argument that I can see us writing for this is to say something about the fact that the three subparts do provide some additional protections and they tend to provide those protections by limiting exposure, by saying there are certain types of research that are not permitted for those categories of vulnerable populations, or by putting -- stressing additional consent requirements. Those are the two main ways.

I think that part of what we add here is to say that those are not the only two ways to provide additional protections, that consent is not the only way, there may be other ways to do it.

Now whether that means one continues to have the subparts or not, what at the very least we could say is that those subparts should be reexamined taking into account this

broader view of vulnerability and additional ways to protect vulnerability. And then some of it could be handled by either eventually revising subparts or by handling it in a more general way.

PROFESSOR CHARO: Jim?

DR. CHILDRESS: Picking up on the sentence that Eric focused on in recommendation 3.11, the -- I am assuming that means that the requirements that we have concerning vulnerable populations as currently existing would be incorporated into one uniform set of regulation. That would seem to me to actually require a lot of very careful work to see -- if you take seriously the analysis of vulnerability, whether indeed we want to do that. I mean, it is just a much more complex matter, I think, and that would just go to your -- to the -- what is under the last sentence in 3.12 that the central office should also issue guidance describing safeguards for different types of vulnerability and there is a bit of a tension there between those and it is obviously a tension, in part, between identifying groups and focusing on types of vulnerability.

But I think a great deal of caution is needed here before we push towards a uniform set of regulations regarding those populations.

PROFESSOR CHARO: Okay. I think what I am hearing is that we need to cautiously move towards a more integrated approach and to the extent that the current form of identifying groups works that we would not want to abandon it until we were sure we had something equally protective but that certainly the

classification of vulnerabilities can be used to help work on other situations in which individuals have become vulnerable by virtue of their status on the particular research at hand and guidance can slowly be developed to try to get more and more comprehensive approaches.

Trish, and then I want to see if we can focus on 3.12's final sentence to make sure we cover that.

PROFESSOR BACKLAR: And particularly because when we lump together vulnerable populations not only are the populations different and diverse but within the populations they are also heterogeneous and so it is very, very complex. One wants to proceed very cautiously.

PROFESSOR CHARO: Finally, in the last eight minutes that we have left, some attention to something that has typically been characteristic of work with what has up until now been called vulnerable groups as a whole. Do not work with children unless the research needs to be done on children because doing it on adults will not get you where you need to go. Do not work with people in prison unless you have to work with people in prison.

This particular recommendation has language that would suggest that we abandon that in favor of a presumption of inclusion so that you would ordinarily include children and you -- I am sorry. You would ordinarily include prisoners, you would ordinarily include pregnant women who were identified as vulnerable, and that the only people who would not necessarily be presumed to be included would be those who cannot consent

for themselves in which case we would be focusing on cognitive issues.

Do we want to move in that direction or do we want to continue the older style of a presumption of exclusion unless people are needed in the research?

Eric?

DR. CASSELL: What you are suggesting is that vulnerability in and of itself, except for certain kinds, is not a criteria for exclusion. I think that is what you --

PROFESSOR CHARO: That is correct.

DR. CASSELL: I like that myself. I think that is a good idea. I think it has to include safeguards but I think it should be inclusive. We are talking about consensual participation on the one hand and we are talking about inclusion in something that is a mainstream activity in the United States.

PROFESSOR CHARO: Diane?

DR. SCOTT-JONES: I agree with what Eric just said. I think it is very important that we keep in mind what we have discussed previously in the commission and that is that access to research is important as well as protection from the possible harms of research. If there are groups that are excluded entirely from research there may be a loss of potential benefits to them because the knowledge may not be generalizable unless they are included at some point in research.

I think one value of the dimensions is that it would allow better decisions about when to include vulnerable persons in research and when not to include them in a particular study because you have a more fine grained way of looking at what the dimensions of vulnerability might mean for a particular study. So I think that the recommendations as they are written seem to allow for the inclusion of vulnerable persons and the only question that I have about the language as it is now is the statement about cognitive incapacity and whether that is intended to include children or whether people might interpret that to include children who do not suffer cognitive incapacity per se but developmentally it is inappropriate for them to make some decisions at certain ages.

PROFESSOR CHARO: I think that is going to be a key issue because there is a lot of concern about whether or not children should be included.

Because the time has gotten so terribly short I might suggest that we try to sort that out with perhaps some alternative formulations that we can mull over with better time.

PROFESSOR CAPRON: Hand up.

PROFESSOR CHARO: Okay. Bill, and Bette, and Alex, and Larry.

MR. OLDAKER: I am not opposed to changing and moving to a more inclusive role. I worry about prisoners since there is such an inequality on the ability of prisoners to make judgments and I, for one, probably would not be in favor of

doing that at this time. It is probably a little too radical if we are trying to get the report. As to children I want to make sure that whatever we do is that they are adequately protected. I am much less worried about someone -- it is not cognitive intent. It is someone who has basically reached, you know, the ability to make a sensible decision. I am not sure if that is 16 or 18 years old but it is not some, you know, kind of bright ten-year-old. And so I think we just have to be very careful. I do not think it is -- you know, the ten year old will have the cognitive ability, I think, under the law theoretically to understand but I am not sure that we should not have greater protections for those children.

PROFESSOR CHARO: Bette?

MS. KRAMER: I am curious about -- I think it was when we were doing the mental capacity report, we heard from -- we heard from several mothers that were representing children who had particular diseases and the diseases themselves rendered the children cognitively impaired. And I remember their pleas to make a provision for those children to be allowed to participate in research because that was really their only hope.

I wondered would they be covered with these suggestions that we are talking about?

PROFESSOR CHARO: I believe that as -- in other areas. This tends to be focused on procedures that offer no possibility of direct benefit to the participant so if you look at the very bottom of the page where 3.12 first appears you

will see that that is the way it is limited. So the idea is not to cut off access to trials in which there might actually be some benefit to the individual participant.

DR. CHILDRESS: Just a clarification. This was written when the report was working with that two part division so --

PROFESSOR CHARO: Right. And this is going to be altered now in light of the tripartite division we now have for the component analysis. Yes.

Alex?

PROFESSOR CAPRON: As you suggested, I am having a little trouble knowing what is on the table so let me just respond on what -- I see a conflict. I see a problem in what I understand to be the interpretation of the present standards and as I understand it the argument is abandoning the present standard on the grounds of access.

I guess my concern here is that we are falling victims to the therapeutic misconception ourselves. Let's keep in mind what we always are saying in other contexts, which is research is research.

If the reasons for including a person in a population is that failure to include them will mean that any products developed, any therapeutic advance developed will be not available to them or not appropriately available to them because there are believed to be unique characteristics to them.

Then already, as I understand it, under present rules there would be a reason for allowing the research to go forward assuming that appropriate protections in light of their vulnerability are met.

PROFESSOR CHARO: Correct.

PROFESSOR CAPRON: I do not see that as an argument, therefore, for changing the rule. I was hearing several people say that the access concern goes to a reason for changing the rule only if we think that it is access to the research as research rather than access to the products of research. And as we talk about all the time, the therapeutic misconception says that access to research is inherently valuable and that is a misconception.

PROFESSOR CHARO: Thank you. And I think actually that is an important contribution to focusing on why we want people included or not.

Larry?

DR. MIIKE: Yes.

PROFESSOR CHARO: And I am going to force everybody to be very brief now because we have reached 12:00 o'clock.

DR. MIIKE: Yes. I mean, I do not know in what form this recommendation is currently but the way it is now it does not in any way grasp what we are trying to say.

What we are basically trying to say is that given appropriate safeguards there is no reason for excluding whole groups of people from research and then there is an exposition about some of the types of safeguards are nontherapeutic

research or not cognitively impaired, the issue about minimal risk, et cetera. So I just want to see what the revised recommendation is going to be because this one does not capture it.

PROFESSOR CHARO: Okay. It may be that it is going to be easier to focus the discussion when we get the language.

I must confess I am sympathetic to Alex's position that in research that is needed in order to understand the population's needs down the road we already can accommodate that by saying that they are now needed and we do enroll them and that this is specifically supposed to be about situations where it is rather gratuitous. But I appreciate Larry's point that in a sense the alternative is to go down the reasonable accommodation approach where everybody is in and we have to accommodate their special needs that are due to their specific vulnerabilities and it is obviously something we are going to need to continue debating as we look at the language.

We have reached the end of the meeting. It has been an extraordinarily productive one. I want to thank everybody and give Eric a moment just to send us off with final thoughts and marching orders.

NEXT STEPS

ERIC M. MESLIN, Ph.D.

DR. MESLIN: Just very quickly as a reminder, please keep November the 22nd on your calendar. We will let you know whether that teleconference meeting is on. That would be a public NBAC meeting.

Secondly, the December 7th and 8th meeting is coming up quickly. Please get your hotel and other arrangements done. Margaret Quinlan will remind you of this but I wanted to remind you publicly.

Thirdly, if you have marked up copies of what are in your books do not leave without giving those marked up copies to staff. If you feel very attached to them, we will take them back, photocopy them and send them back to you if you feel terribly attached but do not leave even if there are scribbled notes. The more we have, the sooner we have, the better.

And then, lastly, on behalf of the absent chair, Harold Shapiro, I want to thank Alta for chairing the session the last two days.

Thank you, Alta.

PROFESSOR CHARO: We are adjourned.

(Whereupon, at 12:05 p.m., the proceedings were adjourned.)

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