45th MEETING

NATIONAL BIOETHICS ADVISORY COMMISSION

The Embassy Row Hilton Hotel
2015 Massachusetts Avenue, NW
Washington, DC 20036

December 7, 2000

Eberlin Reporting Service
14208 Piccadilly Road
Silver Spring, Maryland 20906
(301) 460-8369

I N D E X

P R O C E E D I N G S

OPENING REMARKS

ERIC M. MESLIN, Ph.D.

DR. MESLIN: People have been very patient so I think we will start.

Dr. Shapiro will be arriving shortly but he asked me to open the meeting and to welcome everyone to the 45th meeting of the National Bioethics Advisory Commission.

We will be meeting for the next day-and-a-half to consider two of the reports that are underway and being deliberated about by the Commission.

The agenda for today is to discuss the Commission's ongoing report on Ethical and Policy Issues in the Oversight of Human Research. It is a report that has been underway for some time now and, as Dr. Speers will indicate in a moment, it is a report that we are hoping will be able to be available for public comment later on in this month. That, of course, will depend entirely upon the Commission's discussion today and whether they feel that the report is sufficiently well enough along that it can be presented for public comment.

Just a word about the public comment process. This report when it goes out for public

comment will go out for 60 days. It would go out on our website and it would be mailed out to all those who wish to see it. So for the public who are here and those who learn about the meeting afterwards, it is the Commissions wish that as many people as possible will get access to the report and provide comments to the Commission.

At the conclusion of the 60 day comment period staff will evaluate and present Commissioners with evaluations as well as the copies of the comments.

The Commission will meet again and make a decision as to whether they wish to do more with the report considering the public comments before finalizing it.

I do want to let the public know that at this point we have a Commission meeting scheduled for January 18th and 19th. We have tentatively scheduled a meeting on the 15th and 16th of March. That date has not been firmly established. It is -- we are trying to see whether the Commissioners are available more on the 14th and 15th or the 15th and 16th but we will certainly let the public know well in advance of that meeting.

The second item on the agenda, which will be discussed tomorrow, will be the Commission's report on Ethical and Policy Issues in International Research. We will be discussing proposed revisions

to recommendations. I think everyone knows that the Commission produced a public comment draft that went out on September the 29th for 45 days. Staff have provided Commissioners with the comments as well as analysis and we hope that tomorrow's discussion will provide the Commission with an opportunity to express their views about proposed revisions and where they would like to see them go.

It is not our intention to sign off on or finalize the recommendations since clearly there is textual revisions and chapters to be reviewed. So we are currently planning to have -- to devote the January 18th and 19th meeting to a discussion of the international report.

As with all of our reports, of course, the purpose of having a Commission meeting is to hear what the Commission's views are and decisions are made at these meetings.

With that as a quick overview of what our time table is, I am going to ask Marjorie Speers to both give you a quick run down as to where we are with the report. I think Commissioners have been kept informed of this and the public has known about our work from previous meetings.

Marjorie?

ETHICAL AND POLICY ISSUES IN THE OVERSIGHT OF HUMAN RESEARCH

OVERVIEW OF DRAFT REPORT

MARJORIE A. SPEERS, Ph.D.

DR. SPEERS: Thank you. Good morning.

You have before you in your briefing book a complete draft of the report. That is you have all five chapters now in the report. And we plan to discuss them today.

Since our last meeting we have spent most of our time working on revising the draft report and so I do not have a lengthy update to provide to you today.

In addition to working on the report I did want to make you aware that we have been briefing a number of groups as well as departments within the Federal Government on the draft report. We briefed them based on the draft that had been presented to you in October and we will continue to do briefings on the report upon request.

We have set the agenda today based on what we think will be issues that you want to discuss that are most pressing for you. We thought we would organize the agenda to start with the most pressing issues and then move to the less pressing issues.

So based on that, we thought we would start with Chapter 3 where we need to discuss assessment of risk and potential benefit and handling protocols involving vulnerable individuals.

Then we would move to Chapter 4. I am not sure that there is necessarily a very pressing issue

in Chapter 4. I just wanted to make certain that we had enough time with that chapter since we spent less time with Chapter 4 than we have with the others.

Then move to Chapter 2 and, hopefully, end the day with a discussion of Chapters 1 and 5.

And then we have left some time at the end of the day to come back and look at the full report.

If there are any issues that you want to discuss or if you think we need to move a chapter up sooner for discussion, let me know if we have not organized the agenda the way that you think it should be organized.

Then I think what we will do is we will start with Chapter 3. We have prepared for you and you have it at your seats a document that is simply a summary of the recommendations. If you would like to work from that document, feel free to do so.

And what I would -- I guess what I would propose for Chapter 3 is if you have any general comments on Chapter 3 let's start with the general comments. If not, then I would suggest we move into a discussion of the section on risks, analysis of risks and potential benefit.

DISCUSSION: CHAPTER 3, "POLICY, REGULATION, AND GUIDANCE: SELECTED ETHICAL ISSUES FOR PROTECTING RESEARCH PARTICIPANTS"

DR. MIIKE: It is so good, Marjorie, we do not have any more comments.

Alta?

PROFESSOR CHARO: Yes.

DR. MIIKE: Say something.

(Laughter.)

PROFESSOR CHARO: I sent an extensive e-mail on this point already, which I think you might have there because I had asked Eric to distribute it for you.

DR. SPEERS: Let me ask the group. Do you have Alta's e-mail? If not, I have a copy of it and we can make copies.

MR. HOLTZMAN: I committed it to memory.

DR. MESLIN: The one that was dated December the 2nd.

Alta, I propose that since we have all read it and copies were made available on e-mail, we could just go over them if you like if that is easiest for you.

PROFESSOR CHARO: Sure. I will do my best. I would tell you that the connection is not as good as I have had in the past so I might not catch what you all are saying at times, and I apologize.

DR. MESLIN: Then we will encourage Commissioners to speak slowly and into the microphone.

PROFESSOR CHARO: Thank you.

DR. MESLIN: Because we can hear you just fine.

PROFESSOR CHARO: And you might consider actually going ahead and photocopying them because I am going to have to get on and off this call due to the classes and meetings I have to attend here today.

The e-mail that I sent last week or earlier this week went through a number of recommendations where I had suggested changes and with Chapter 3 it begins with Recommendation 3.1.

Specifically 3.1 is a recommendation where I would suggest beyond simply on a writing level trying to keep things a little clearer that we recognize that there are often three components and not just two components to research studies in the clinical trial context and in the redraft that I had proposed I tried to make it very clear that I was talking in this case only about clinical research trials.

As Marjorie has said, there are components that are designed to answer a research question and offer no prospect of personal benefit with a paradigmatic case being, for example, to simply observe somebody in an MRI not because you are thinking you are going to pick something up but because you are looking at how something appears to be effective in certain neurological activity.

A second might be components that are designed to answer a research question but also offer the prospect -- as we have put it in the past -- the prospect of a direct benefit to the research

participants and these might be components where, for example, you give somebody a drug that has been shown to be therapeutic in another context.

But there is a third component which is often present and that is often there is a purely standard therapy that people are being offered. In other words, they are going in for a series of standard treatments with a research add on and I wanted to clarify for the purposes of this recommendation that such a third component does exist. And simply to say that for those third components in the clinical context where it is a standard therapy that the role of the IRB is simply to make sure that there is no real substantive difference between the study population and the kind where this would ordinarily be offered as standard therapy but they are not supposed to be acting as if they were a review board for a professional society reevaluating the standard therapy.

DR. SPEERS: Alta, this is Marjorie.

In the text on page 18 we made an attempt to deal with standard procedures that might be offered during research and we had -- in one draft had created a figure that had a third column to deal with the standard procedures and as we started to work with different standard -- with standard procedures and the different ways that they could be used in research, we thought that it was better to address

the use of standard procedures in the text and not to include a third column in the figure.

And the reason for that was we could identify three different purposes of standard clinical procedures. One purpose of a standard procedure could be simply to answer the research question and if that were the case then those standard procedures would go into the column relating to procedures designed solely to answer the research question.

Other standard clinical procedures could be used -- could be part of those procedures that answer the research question but also provide the prospect of direct benefit, such as in the case when interventions are compared and an experimental intervention is compared to a standard procedure.

In which case those would go down the column of those procedures that offer the prospect of a direct benefit.

And then we acknowledge that there is research where standard procedures could be offered but they are not part of the research. They are not part of the research and in that case they would not go down either column in the ethical analysis that is done that if those are standards procedures used as they ought to be used for clinical practice they do not fit into the ethical analysis.

So we tried to deal with that issue in text.

We may not have dealt with it sufficiently there and maybe we need to include some of that text in the recommendation.

PROFESSOR CHARO: May I respond?

DR. SPEERS: Sure.

PROFESSOR CHARO: I appreciate the effort, although I think we would all agree that we would never want the decision about either text or recommendations to be driven by what is easily presented in a figure. I am sure it is not what you are suggesting.

My experience on IRBs has been that one of the trickiest areas has always been in the area of clinical trials that are combining background standard therapies with an additional set of standard therapies that are then to be compared to one another with yet another component that is purely for research purposes that offers no therapeutic value at all.

And my goal in the rewritten recommendation 3.1 that I had distributed was to try and tease them all out in the recommendation, again because my experience has been that the recommendations are often read in isolation, in an effort to make it possible for IRBs and investigators to clearly and succinctly see all of these different kinds of strands and appreciate the different ways in which they are each reviewed.

One of the hardest things to do is to persuade investigators who are looking at comparisons of standard therapies that they are actually doing research. I think many of us on IRBs have had that experience. The persistent calling of the participants as patients rather than subjects or participants bespeaks the kind of mind set that this is not research that needs to be reviewed. This is just us giving our best shot in various ways.

I do not understand why there is a real problem in more completely reflecting the reality of the research protocols that people are reviewing and more completely giving directions to the IRBs since the rewritten recommendations specifically tells the IRBs that the -- you know, the nonresearch focus component that a standard therapy are not to be reviewed the same way, and it says exactly how they should be reviewed instead.

DR. MESLIN: Bernie?

DR. LO: I think Alta has put her finger on a real problem with clinical trials in this country which is very analogous to what we have been debating in the international report in terms of level of care provided to the control group.

There are some types of clinical trials where it is disturbing in a sense that care provided during the trial is standard care in the sense. It is what is customarily available in the community but

it falls below the standard of care of what a good doctor or good institution will provide.

For example, in many cardiology trials the comparison is between usual care versus usual care plus an additional experimental intervention.

PROFESSOR CHARO: Right.

DR. LO: The problem with usual care is that we have many studies documenting that the usual level of care falls short of what is proven to be effective and established.

Investigators commonly argue that the real research question is whether if you take what now goes on in the community and add something else, is that better?

IRBs have a lot of trouble sorting out is that a legitimate study. It is the same question we face in the international trial. Is the research question relevant to the population being studied? And you can look at it one of two ways.

The other types of studies that are very tough to sort out are sort of quality improvement trials where you say, "Look, we know things are not very good. What we are going to do now is do an intervention that is going to improve what actually goes on. Put in a new information system or something like that but we want to do it more than just a quality improvement thing because we think it is really generalizable so we are going to send it to

the IRB."

Well, you know that in the course of that trial people that you are going to be enrolling as participants are going to get less than -- I am not going to say optimal care but less than the standard of care in the sense of what a reasonable physician ought to do in the circumstances.

And so it is kind of the investigator knowingly entering people into a clinical trial where they would not want their grandmother or sister getting that type of therapy. And, you know, to me it is very analogous to what we decry in the international setting.

My point here is that this -- you know, the problem -- well, the problem and the strength of our report is it will apply to a whole lot of situations that we may not have thought through. I am concerned about saying something, you know, as a recommendation that clearly is right in a certain set of circumstances but it is going to be -- that language will also be implied in other circumstances where we really cannot -- we may anticipate those circumstances but we have not really thought out the sort of line of thinking.

So I would be -- I mean, I think -- you know, there is a lot that is attractive about this division that, you know, really goes back to one of the Commissioned papers but it is really much more

complicated than that in clinical trials and I would say that particularly in clinical trials that try and address real practice, trying just what is actually going on in practice as opposed to an efficacy trial which is sort of a hypothetical best world situation.

DR. MESLIN: Alta, did you want to respond to that?

PROFESSOR CHARO: First, I would like to thank Bernie for the comment because I agree with him and second I would like to also offer an additional observation.

If the goal here is to move towards a component by component analysis, one of the things that IRBs are going to face in trials that have all three of these aspects that we recognize exist in the clinical -- let's say a clinical drug trial context, it is whether or not they are going to be looking at the components that are therapeutic and designed to answer the research question separate from the therapeutic components that are not designed to answer the research question or if they are going to combine them when they do their kind of risk/benefit analysis.

An additional advantage of more completely separating these strands would be to clarify that on a component by component basis that standard therapeutic interventions that are there just as background for the trial, just as an adjunct because

these people need these therapies at the same time that they are in a trial, those components are not going to be added into the benefit section of our component analysis when we look at the specific research intervention that is being evaluated but that intervention's risks and benefits will be analyzed on its own.

By the way, as an additional just an aside comment, another thing that went on in the suggested redraft was to remove the word "research" -- the phrase "research equipoise" from the recommendation as per the conversation at the last meeting and substituting "substantive definition" of it in the recommendation instead of using the phrase to make sure everybody understood it right when they read the recommendation.

DR. SHAPIRO: Alta, it is Harold. I have just walked in. Thank you very much for joining us.

I really -- I walked in obviously in the middle of this discussion of recommendation 3.1 and I am not sure I fully have caught up yet with exactly what issues, Alta, you and Bernie were trying to get at but I will leave that for later and I will have a chance to speak to you both and hear other Commissioners.

I take it we are focusing now on 3.1 which deals with the so-called components analysis of the suggestion that these trials be dealt with on a

component by component basis, and I have a question I would like to ask. If it is redundant or has already been dealt with, please tell me. I ask the Commissioners to just tell me and I will just catch up during the break.

On the -- there are many -- to me there are some very attractive aspects to this component by component analysis. Particularly attractive to me is the fact that by putting in a component there where there is so to speak no direct benefit or where it is solely a research question, whatever the phrase is we use here, really highlights very clearly that difficult decisions that IRBs have to make. It does not enable you to just imagine a benefit and sort of justify it on that basis alone. It has a benefit of really highlighting a difficult decision and I like that.

However, the question is what does one do -- maybe I should pose, Marjorie, the question to you -- with the fact that these components are interdependent? What we are going to do with the fact that they are not easily compartmentalized always. As you look at various trials it will be very difficult to know which is which and I am just asking a question as to how does one deal with that issue.

DR. SPEERS: This model would require the IRB to force the procedures into one category or the

other. As it is proposed now it does not allow for components that might be difficult to classify. It says they need to be classified one way or the other.

The advantage that I see to that is particularly with components that are -- let me back up and say I think it is a good model in the sense that it really forces the IRB to look at each of the components and decide whether they might offer the prospect of a direct benefit or they do not and to make that judgment. If an IRB wants to say, well, this component is mixed, it may do both, then "mix" sounds more to me if that is the case that it probably fits on the side that it may offer the prospect of a direct benefit.

The criticism that you might have of that is that IRBs could then put more things into that category than they rightfully should put into that category but it really does force the IRB to work with the two categories.

DR. MESLIN: Alta, it is Eric. We have now distributed to the Commissioners your e-mail so if you did want to direct anyone's attention to that, and I apologize. We will try and make sure that the public at least knows what we are talking about at some point as well.

PROFESSOR CHARO: Thank you.

DR. MESLIN: I apologize.

DR. SPEERS: May I comment? May I? Okay.

two things. One is I think that the point earlier that Bernie was making might be a bit different from what Alta was making, and I just wanted to point that out. I think that Bernie is making a very important point that many clinical trials are set up as you described them where one arm of the trial is usual care and the other is usual care plus something else, and so the question arises as to how should that be analyzed.

I think that under this model that type of study is covered in the sense that that type of study would be analyzed according to the -- it would be analyzed -- it would be classified as procedures that answer the research question and also provide the prospect of a benefit.

What we say in that case is that the analysis that should be done is to look at the risks and the potential benefits for each of those procedures and they are meant to be compared against what is considered standard practice.

So if in the "control arm" that is getting usual care, if that is less than standard care then the IRB could make that judgment and say that that particular trial should not go forward.

The model, and I think as we have written it, takes into that -- takes that situation into account. Now whether an IRB is willing to make that kind of a judgment is a different -- I think a

different question.

PROFESSOR CHARO: Hand up.

DR. MESLIN: Bernie and then Alta. Larry, sorry. Bernie, Larry, Alta.

DR. LO: I guess I feel uncomfortable because, you know, I sort of throw this out as a specific example which seems to strain the analytic framework that we are advocating in recommendation 3.1. And I guess I -- I do not know, maybe I am just sort of getting too old now but I really am concerned about making a general pronouncement without really having had a chance to really think through all the ramifications in lots of different situations.

I guess the concrete suggestion I would have would be to soften recommendation 1 and rather than saying they should issue regulations requiring IRBs to use this analytic framework, nor should explore the usefulness of this framework in sort of helping IRBs make these complex determinations but make it more that they are going to think about it and really, I think, draw on the expertise of people in IRBs who can come up probably with many more sort of situations they deal with than we can and say, well, you know, this kind of works here but it does not work here, here and here.

I am really -- you know, we have been very critical of the current regulations for sort of applying ideas that work for some biomedical research

and lots of other types of research, and I am just concerned that by sort of setting out in a recommendation like this a general framework without having looked at how it affects different types of research, we may be doing some harm as well as good and maybe we need to sort of throw it out as an idea to be considered rather than something that must be adopted and that IRBs may follow.

DR. MESLIN: Larry?

Alta?

PROFESSOR CHARO: First, I do not actually -- I do not oppose Bernie's suggestion. Actually I think the public comment period could be very valuable in getting IRB feedback on just this point.

But let me propose a concrete example that would raise the kinds of issues that are being raised in the discussion so far. Imagine one wants to do a trial of some new medications for the treatment of obesity. You could imagine a trial that has three very distinct components and it is going to be a little variation on Bernie's.

Everybody has to go through the Dean Ornisch exercise and low fat diet so we would call that the standard component and it is the background because everybody should be doing it and it has lots of benefits and very few risks.

And then for the study participants there is now a research intervention with the prospect of a

direct benefit. Some are going to get fenfluramine and others are going to get fenfluramine and phentamine together. The old Phen-Fen combination.

And then that will be the research intervention that offers the prospect of direct benefit using a variety of already approved drugs in various combinations.

And then there would be a third component that has to do with purely for the research purposes some kind of psychological test that is not used to diagnose depression to treat people but simply to kind of keep track of people's moods.

Now the question I have is whether we want to very clearly tell IRBs that when they are looking at the risks of the Phen-Fen combination or the fenfluramine alone that they should do that risk/benefit analysis, that is the prospect that those drugs will drop your weight with all the attendant benefits versus the risks of those drugs. Do you want that component analysis to be done with the benefits of the Dean Ornisch diet included or not?

The reason I suggested the rewrite that I did is because I was suggesting that we want to make sure the IRBs recognize that the standard therapy, the Dean Ornisch diet, is excluded from that risk/benefit analysis and you look at the drugs in and of themselves. And you do not add in the

benefits of these background standard therapies that everybody is getting.

That is the kind of example I have in mind so Bernie is right. It is usually standard therapy versus standard therapy plus or it is standard therapy for everybody with different kinds of plus factors distributed across the population of study participants.

DR. MESLIN: Larry, did you want to comment now?

DR. MIIKE: Yes. I think, you know, that as currently written the current recommendation does have sort of an ease out statement at the very end about issuing guidance and clarifying the application. I do not think we are ever going to find any way in which what we say applies to every possible situation so maybe the way to soften it is what Bernie is suggesting.

But, I think, the basic reason why this recommendation is there is we want to talk about research that offers no direct benefits and research that offers direct benefits. I think we are getting lost in the discussion that is going on right now.

Alta, your suggestion then on adding even a third component to this leaves me a little puzzled because what I think you are saying -- now that I have your written things in front of me -- you say -- you asked a question about whether in your third

component, whether that standard therapy should be even permitted because that is a question that you asked the IRB to take a look at and that sort of puzzles me.

PROFESSOR CHARO: No, that is not my intent. The intent was to have the IRB only check that the standard therapy is being offered in the standard way. If it is, that is the end of the IRBs review.

DR. MIIKE: Well, just all I am saying is that the way it is currently written you are saying that it should be permitted and it just did not make any sense to me at all.

I agree with you that -- I guess ordinarily if there is going to be a standard therapy being offered, so is the control group, right, because the difference is going to be in the additional experimental --

PROFESSOR CHARO: Not always. Sometimes it is a backdrop to a variety of different research interventions so it is not a control group that is getting it. Everybody is getting it and then --

DR. MIIKE: Right, that is what I meant. I meant that they are not getting it exclusively so it is a background issue. It is not an additional benefit or an additional therapy component, right? It is a background so that everybody else has it.

PROFESSOR CHARO: Yes, it can be.

DR. MIIKE: Yes. So I still do not -- I do

not see why we need a third component. It just sort of muddies the water for me when we start to do things like that. But anyway my point is that the intent is simple in this recommendation and we are starting to get it too big already. And then my general reaction also to these things are that these are getting to be extremely long recommendations. And I know that the reason behind that is that we are deathly afraid that people will only read the recommendations. Well, my answer is tough luck. I mean, if people just want to read the recommendations and make decisions on that then I say tough luck. You know, that is what we have reports for.

DR. MESLIN: Jim?

DR. CHILDRESS: Well, I do not know how to follow that one.

(Laughter.)

DR. CHILDRESS: I think I would like to build on that and Harold's query about the interdependence and interrelation of the components. And without being able to answer it, just to further push the question because I guess Marjorie's response that we need to force these components into particular categories is in some ways troubling to me because that -- the kind of notion of forcing may suggest again the way in which certain features get cut off and it may miss some of the interdependence and interrelation.

Now there are examples in the text of how this analysis would be used but I guess I am not clear from even those examples, and I need to look back over them again more carefully perhaps, sort of how this analysis in the final analysis really ends up sort of now helping us do a better job in thinking through the issues. I guess I would end up at this point in the discussion supporting Bernie's suggestion for the way we reword and redirect 3.1.

DR. MESLIN: Alex?

PROFESSOR CAPRON: Well, I am at a disadvantage in that I do not have Bernie's suggestion or I missed it having come in after it was stated.

The general approach of differentiating the components so as not to fall into the trap of labeling a project as a whole, one thing or another, but to recognize that the research component is the central focus of the IRB strikes me as a good one.

In looking at Alta's suggestion I do not believe that if there is a distinction between two and three that three is limited to clinical medical trials. It would certainly be possible in other kinds of observational studies, psychological studies, educational studies and the like to have some things provided as a purely beneficial intervention.

I do have a question about what this

division into the components means for things which are potentially of some benefit, however, because in Alta's description the -- that category are to be evaluated for their benefit to the individual and it seems to me that if there is a research intervention which has a prospect of benefiting the individual but it is also a research intervention that the benefits to society are equally relevant on that scale and we should not take that more radical step of saying you can only count the benefits to the individual.

I finally have a question about -- and this is sort of -- this is a version of what Jim may have been getting at with his statement about the interactions.

We know that now that so much clinical research has been moved into physicians offices where it is run on a contract basis for contract research organizations and the like that many people regard access to interventions which are of unproven benefit but which offer, they believe, the only prospect of treatment for a disease or at least the only prospect of treatment that they can afford or have access to given their insurance status as beneficial.

And I realize that this may be something that is in the second category but in some ways that -- the risks there are largely the risks of the therapeutic misconception and I am not sure whether this division into the different categories in the

end will help us to see that or obscure it for IRBs.

So I am inclined to have the division but I think, as Jim does, that we may have some problems here and perhaps Bernie has sorted this out and is there a written version of the -- of your comments? No, these are oral suggestions.

DR. MESLIN: Larry?

DR. MIIKE: I am assuming that -- and maybe it is not clear in here but I am assuming that all -- everything is asked the question about solely research and then in addition to that if there are prospective benefits in the research that you add the -- ask the additional question. It is not an either/or choice, right. That is what I am assuming.

DR. SPEERS: That is correct. I mean, in terms of the analysis, and I think that one of Alta's suggestions is a good one and that is even when we are describing the procedures that also offer the prospect of direct benefit that we say in the recommendation they also are intended to answer the research question. We need to make that clear.

There was a suggestion -- I want to give Harold credit for this suggestion. It is one that he had given me before the meeting that I think is important and might help to summarize some of the discussion here. And that is for us to strengthen in the text that this analysis that is done is a really difficult analysis for IRBs in many types of studies.

It is particularly difficult when IRBs need to judge the risks against the potential knowledge that will be gained because we do not know whether that knowledge, in fact, will be gained for the research. It is the expectation that we will gain knowledge.

But as Harold said, particularly in studies that involve high risk, and it was Alex's last comment that made me think that this was relevant to say, particularly in studies involving high risk that is a very difficult decision for IRBs and we do not want to overly simplify it by not acknowledging it and so perhaps we could strengthen the text to say that.

DR. MESLIN: Bernie?

DR. LO: I also would find it very helpful if we could have an example of the type of protocol where this analysis proves superior to the type of analyses the IRBs might do today. So what I am missing is a real sort of -- I am thinking as sort of an IRB member. Show me how this is really going to help me with the tough cases I know I have to deal with.

DR. SHAPIRO: It strikes me on this issue that we are struggling with -- let me see. I have a very particular question.

Alta, let me ask you a question. In your rewrite you talked about balancing -- the risks are reasonable and are balanced by the perspective

prospect of direct benefit to the research participants. This is in the arm which -- where there is some potential benefit.

Did you mean that in language to eliminate other possible benefits?

PROFESSOR CHARO: No. Actually I was only trying to deconstruct the meaning of research equipoise as best as I could understand it from the text.

DR. SHAPIRO: Okay. That is helpful. Thank you.

I mean, I think my own judgment is -- I mean, I agree with Alex and others who think that this division is, in fact, quite useful and we just have to make it works in ways that are sensible and so on.

I think myself one of the hardest issues is to deconstruct the various parts of the trial and decide which arm it goes into, which is one of the reasons I raised the issue before. I think that is a very difficult moment at least as I understand it. I do not do any of these trials so I do not have the practical experience but that is difficult. But maybe Bernie's suggestion to try to provide some examples might be really quite useful in that respect.

I do believe, as I look at this, one of the great benefits to the IRBs is that it really poses

the questions in a starker manner and does not enable one to say something very general about, you know, potential benefits to society and somehow not force you to look at the real risk that individuals are taking on in some cases. I think that is a side benefit that is not directly related but I think it is a side benefit here.

So I think with respect, Bernie, to your issue of not being able to get -- capture easily all the, you know, various shadows -- there are lots of sensitive issues here, not only sensitive but difficult and complex issues, which cannot be put into any single recommendation that had some kind of finite length to it. I agree with Larry. Some of these recommendations do get on.

I think we should not -- we might want to soften the language some but I do not think we should soften it too early. I would like to get some feedback from this -- from the community out there who understands clearly what we are saying and we have opportunities. I think it would be very wise as we go along to soften it. I do not want to do this too early. I want people to focus on the issue and get us some feedback.

PROFESSOR CAPRON: Let me try taking up the question that Bernie raises. And I think that the component analysis is important in two ways. One, it asks us to deconstruct, and I do not think the word

"arms" is what we mean because "arms" suggests the person getting -- A versus B or something. But it is really if you deconstruct it, it then has a consequence as I understand the thrust of this, and it is a very big consequence and we may not mean to say this.

Let me take an extreme example. If someone designed research which had a high degree of physical or psychological risk to it and offered people a large amount of money to do it, $10,000 for participation in this research, which has a substantial risk of death, I think most IRBs would be very concerned about that and they would say only if there were a very high benefit to society and a very good consent process and very good screening that we were not just picking people off the street who -- I mean, literally off the street, who -- for whom $10,000 is the difference between life and death itself, would we even consider doing this.

But change the example and now have this be that what the people are getting is a medical treatment which they believe is also a life saving thing to them. Not -- and we are no longer dealing with poor people. We are dealing with sick people. And we look at that and we say because they are coming into this study which has a component that runs this high degree of risk they are also going to be getting a medical intervention which they could

not otherwise afford and which they believe offers them a prospect of overcoming their illness.

We -- I think it is true, Bernie, that some IRBs today might be inclined to say, well, this is therapeutic research and, therefore, the benefit, the potential benefit to the individual justifies the level of risk involved.

The idea of separating those is to say if the part that is so beneficial is a standard treatment which you are giving people and is not part of the research component but is simply something that you believe or you argue have to go along with it, this component analysis would say you must in deciding whether or not to allow the research to go forward, if it is the research intervention that runs this high degree of risk, evaluate solely the benefit to society from that research component and exclude from your analysis in that balance the benefit that comes from getting this other component because it is as though it were just offering someone a lot of money to induce them to come into the study.

I mean, it is really no different. It is not something that is being studied here. It is not something new. It simply amounts to an inducement. And if it would be in terms of the knowledge gained inappropriate to have people run the risk then that is a study where you would not permit the study to go forward. That is what the component breakdown does

it seems to me. It says we should not allow our thinking to be muddled by things which are not the research component simple because they are beneficial.

DR. SHAPIRO: Bernie?

DR. LO: Yes, Alex, thank you for that. But then my question is, is this recommendation really addressing the issue of research in the clinical setting that offers an intervention that has a moderate amount of risk to the participant and the potential of direct therapeutic benefit? So are we dealing with a rather limited subset of problematic cases for IRBs or giving them a standard that is so broad that it is going to apply across the gamut? That is what I am having trouble understanding.

PROFESSOR CAPRON: Well, I do not see the harm in that actually. I mean, if IRBs got into the habit of looking at something and saying this is the nonresearch component that both arms are going to get and then here is the research intervention, that is what we are going to evaluate for its permissibility in light of the potential benefit to knowledge, is it reasonable and then all the questions about selection of subjects and informed consent follow.

It does not seem to me that that is particular procrustean. That is to say that in situations -- and I do not think it is just medical. I mean, it could be educational. It could be

psychological. I mean, the notion that the only kinds of interventions in which benefit is offered are clinical medical ones I think is wrong. There are times when people are doing studies that they offer something which is a standard intervention and not just a medical treatment that is designed to offer some good to the people who get it.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I would concur with Alex, Bernie. I think it is a general conceptual scheme that says you cannot do your balancing across the whole. You split into the components and you say I weigh this component and it does not matter how much other benefit may come from something that is logically distinct. And I think, for example, the money is a very good way to put that.

It is to help IRBs to clarify their thinking and to say a certain kind of balancing you may have done in the past should not be done. And the question maybe is in terms of the text and it may already be there, to take an example, right, which says if you analyzed it in the old holistic model you might be led to conclude this was okay but, in fact, you have just mixed apples with oranges.

DR. SHAPIRO: I agree with these comments. This is a significant recommendation if we should eventually decide to recommend it. Just what form it takes is still up for some discussion but it is

significant.

Marjorie?

DR. SPEERS: I have just been asked to summarize where we are on this so we can move forward.

I think what I am hearing is that I think there is general agreement to move forward with the component approach. There is some hesitation and I do note the hesitation. What we will do is I would like to rewrite this recommendation to do a couple of things. One is to make the components that also offer the prospect of direct benefit, to say that they are also there intended to address the research question.

I would like to remove the term "research equipoise" from the recommendation and explain it so that it does not require one to understand what equipoise means.

And then in the text we will add to the text -- we will note that there may be -- it may be difficult to categorize components because they may have a mixed intention and not easily be categorized so we will acknowledge that.

We will talk about the difficult decision that IRBs need to make, how difficult the decision is in analyzing risk and potential knowledge gained from the research.

And we will put in an example of how this

model is better or potentially is better in terms of protecting participants.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: I also wanted to respond to Larry's somewhat familiar refrain about recommendations. If the recommendation says everything that you just -- if it addresses -- I mean, some of what you described was text.

DR. SPEERS: Right.

PROFESSOR CAPRON: But if the recommendation addresses all the points here I see no harm in its being -- taking up as many lines as it needs to do that, I mean. And it is true that we need text to explain but the notion that recommendations, shoulds and wills and so forth belong in the text and people can find them there, I just disagree with.

On the other hand, I do think if we are going to use this it would be helpful not only for the recommendation but for people who come to use this as short-hand to give them a short-hand. So if we are giving the -- if we are having these categories, let's find names for them so that we do not have to repeat the phrase "those designed to answer the research question and offering no prospect of personal benefit to the participant," blah, should be...et cetera, et cetera.

DR. SHAPIRO: That was read with feeling.

PROFESSOR CAPRON: Yes. So if we could call

-- I mean, call that the research component or the research only component or something that you can have in two or three words something that now takes eight or ten every time it is used, that will become the short-hand and IRBs will use it. Now we are talking about the research component, now we are talking about the potential benefit component or whatever it is.

DR. SHAPIRO: Thank you.

Larry?

DR. MIIKE: I cannot let that go without saying something. Of course, I agree that we have to be able to state in the recommendation what we really mean. It is just that my general proposition is that every time we go through these things they just get longer and longer and longer.

DR. SHAPIRO: The EK theorem.

All right. Let's then -- Marjorie, why don't we move on and take on some other aspects of this chapter now and we will come back to this when we look at some rewritten material?

DR. SPEERS: In this chapter -- in this section there are two additional recommendations, 3.2 and .3. Do you have comments on those?

Alta had a comment which she may want to mention.

PROFESSOR CHARO: On 3.2?

DR. SPEERS: Yes.

PROFESSOR CHARO: Yes. In 3.2 there was a phrase in it that said something about when a research study involves a high level of risk or unknown risks that should be reviewed by a national panel, da, da, da. And I had suggested deleting and simply substituting "nor should create a mechanism for national or regional panels to be used for reviewing research that presents special considerations."

The reason for that suggested change is that there is no such thing as a "high level of risk" in the regulations as they currently exist and although it appears later on in 3. -- I think it is 10 -- I found myself strenuously disagreeing with the creation of that new category of risk and so I did not want to see it referred to here because it had no definition, and simply suggest that the new office create some mechanism that is more flexible and generally offers central or regional review for a variety of special problems.

DR. SPEERS: Bernie?

DR. LO: Yes. I strongly agree with Alta's concerns about that last sentence. Not only do I not know what a high level of risk is, I think all research involves unknown risks. Our IRB makes us put that into every consent form. There are all these risks and then some we do not even known about yet.

I would also be concerned about requiring review by a national or regional panel. I would like to be much more flexible. I like all this formulation. And in addition to review, I think often IRBs benefit from just talking out the issue with someone who is then not going to turn around and regulate them. I think that we heard this from, you know, one of our panels a number of meetings back so I would like to have some mechanism for helping IRBs think through these issues, these special considerations as Alta terms them, but to be very flexible about what should go before them and what kind of mechanism that is, whether it is required or optional review versus consultation.

DR. SPEERS: I think it was Larry and then Jim.

DR. MIIKE: I agree with both the previous people. I get a little leery when we establish a national panel because it gives an excuse to bump a decision away from where I think it should really be done, at the local level.

DR. CHILDRESS: I agree with the proposed change and I guess I would wonder, though, since this is now being broadened to, and I think rightly, to deal with a variety of special considerations, whether there is any particular reason for having it here in the context of the discussion of risk?

DR. SHAPIRO: I just want to focus and make

sure I understand how the Commission feels on an issue that has not been raised and perhaps it is not an issue but this recommendation contains an idea of what we think of as sort of normal risk, the every day risks so-called to the general population. I am just wondering if everyone is comfortable with that and the chapter that deals also with vulnerable populations as the right standard it seems to me is an important issue. I just want to make sure I understand where the Commission stands on that issue.

Bernie?

DR. LO: In response to that, Harold, I would like to suggest a slight change in the sentence beginning "even though studies may not all be minimal risks to subjects in the general population, where participants with vulnerabilities are involved the IRBs need to determine whether it is still minimal for those individuals." I mean, what we are really doing is saying there is minimal risk for people in the general population and it may not still be minimal applied to a special vulnerable population. You need to sort of think about those separately.

DR. SHAPIRO: Arturo?

DR. BRITO: I agree with Bernie but I think I would take it one step further because I had -- this same sentence I had some concerns about because in the text it is nice to describe some specific examples given about special or vulnerable

populations in specific circumstances and when you read the recommendation with the sentence in the recommendation it gives the impression that a vulnerable population in any study is going to require added -- is going to be placed at even greater than minimal risk even if it is minimal risk, and I do not think that is what it is meant to say.

And I had thought about some ways to write this and one of them is to say something on the order of something like this: "However, when potential participants have specific conditions that renders them more vulnerable in a specific protocol..." something of that order, then they would be considered -- this protocol would be considered greater than minimal risk for that population. Something of that sort. I think some rewording is needed here.

And I am not sure how this now relates because I agreed with Alta's changes, too, and somehow this is all interrelated but I have not had a chance to think about that now.

DR. SPEERS: Okay. I think Steve and then Alex.

MR. HOLTZMAN: So with respect to the deletion of the last sentence and a replacement with something in the form of Alta's recommendation, I would like to endorse that with -- and endorse Jim's observation that it is not just about risk. So I

think that in moving it separately and providing such a mechanism is a good idea.

With respect to the standard now of risk, going back to Harold's observation, I just want to test where we are because in setting the standard it cuts two ways, right. The first is the one that Bernie and Arturo is addressing, is that having said that the standard of risk is one that normal population recognize, and I am going to try to avoid the word "vulnerable" for a moment, but in certain circumstances certain people given the nature of the condition or whatever will be more at risk and you just have to recognize that.

I think we would all agree with that. I think we would all agree with that.

It is the other one that I think we need to test, right. We have the example of -- get away from a child -- just an adult who is daily taking chemotherapy, right, that is their normal day-to-day life, are we saying that when we assess whether a procedure is risky for him or her, our standard is the person who is not getting the chemotherapy every day? We struggled with this before but that is the implication of what we are saying.

DR. MESLIN: Alex?

PROFESSOR CAPRON: To go down the list of topics that are now before us, I agree with the removal of the special panel to elsewhere. It seems

to me it ought to go under the description of the authorization of this new research ethics office and it could be one of the powers, in effect, that the authorizing legislation would give, which is the power to establish national or regional panels and to issue regulations specifying when protocols must or may be brought to such panels. And there are then in the text discussion of what that would mean.

I also agree with the rewriting of the sentence about the full IRB review. I had rewritten it, Alta, the same way except I had left the word "all" in. "All research studies involving greater than minimal risk should be reviewed by the full IRB."

This question of the vulnerability, I think Steve's elaboration on what Arturo said was a good one. I had tried writing it simply by saying whether the level of the risk is the same for these individuals, those with particular vulnerabilities, as for participants without these vulnerabilities. I mean, I think that is what we are trying to get to.

On the question that -- the last question that you identified, Steve, it seems to me that the purpose of the thought, both in the first sentence and the one we have been talking about, is to say that the evaluation of the appropriate definition of minimal risk is a population-wide definition but the evaluation of whether subjects are within that

category is a category of subject definition. That is to say it is not an individual definition because the IRB is not reviewing individuals but it is a question that if this is of minimal risk for adults but of high risk for children then it moves out of the minimal risk for the children and has to be reviewed differently.

I believe that for all the reasons that we rehearsed when we first visited this issue around the interpretation as it then was of the present regulations, which are regarded as ambiguous on this question, but where OPRR had made an interpretation, that is correct to say minimal risk ought to be defined on a general population basis.

It is true that some people are used to encountering greater risks because they have to undergo very dangerous treatment because of their illness but it amounts to an invitation to direct research that does not have to go to those populations to them if you say you can boost up the level of what is minimal risk for them because after all they are already under the gun all the time. And I think that that is a step that we ought, in line with the interpretation of the present ambiguous regulations, to ask to be made clear in future versions of the regulations. That is what the first sentence does and I think it is correct.

DR. MESLIN: Bernie?

DR. LO: Yes. I think Steve and Alex are starting a very important and fruitful line of discussion, and I think Steve raises a good point in terms of how we interpret minimal risk the other way.

First of all, we have to keep in mind what the impact is of saying that something is minimal risk. We are going to recommend that minimal risk research be eligible for administrative IRB review. So it takes it out of the detailed scrutiny that would ask the tough questions about Steve's case, I think, we would want asked. Because what happens -- what I see happening there is a tendency to say, well, why do I have to have an extra bone marrow? Why can't I just wait and take a little bit extra sample in three months when they are scheduled to have a bone marrow for clinical purposes?

That is the kind of probing question, I think, an IRB may raise that may not come up in the administrative review so I would like not to be able to say that something is minimal risk for a special population even though it is greater than minimal risk for the general population for that reason, as well as the reason Alex articulated, which is then you just start doing more research on vulnerable people because sort of they are used to anything.

DR. MESLIN: Rhetaugh?

DR. DUMAS: I think we should be careful to be consistent in our definitions and I recall in a

previous report we spent quite a bit of effort defining levels of risk, minimal and greater than minimal. And, if necessary -- if it is necessary to alter that, I think we should provide some guidelines for determining when the level of minimal risk, what kinds of conditions, examples of conditions or situations where minimal risk would be bumped up to greater than minimal risk so that there will not need to be qualifications on the definition in the various documents that we put forth.

So I would suggest that we make very sure that how we are using the term now is consistent with how we have used it in previous reports.

DR. MESLIN: Trish, do you want to speak to that issue? You are on next anyway.

PROFESSOR BACKLAR: Yes, I do actually. Yes, I think it is extremely important what you just said, Rhetaugh, and that is that we tried very hard in our Capacity Report not to have these three levels of risk and minor increment over minimal risk. We want to be extremely careful not to add this third wishy-washy level where we will not know where we are or the IRB will not know where they are.

I also want to go back to say something that Alex said, which I -- which we did consider and we were very concerned about it in the -- when we were discussing issues to do with vulnerable populations Capacity Report, and that was something that actually

the National Commission addressed in terms of when they were discussing about children in research. And one of the Commissioners, and I forget his name but, Alex, you probably do know who it was, was so concerned about putting forth a recommendation that would allow for people who were ill to have more research done on them and I am very, very concerned that we make sure that that does not happen here.

But I know this is a three part discussion.

As I look at these recommendations and I see the discomfort of having -- talking about the national -- about NORE. I see that we have -- NORE is referred to in many of these recommendations and I am presuming, Marjorie -- let me ask you this: Is that because you want to make sure that in every facet of this so when you are looking at risk or whether you are looking at the components that you want to bring in that NORE should be part -- that people can go back and NORE should participate in this?

I want -- if that is your intention, if you take that out of here, would you be able to smuggle it back in when -- if you keep NORE out of reach of the recommendations? Can you do that?

DR. SPEERS: The -- our thinking was -- that was our -- that was where based on the last meeting we had intended to go, was to not put NORE, if you will, into each of the recommendations. But on

further thought, each of these recommendations in a sense should be able to stand on its own. You know, that someone might just pull out 3.1 and want to look at 3.1. And if that is the case then, in effect, each recommendation needs to be self-sufficient. It should state who does what. Who is being recommended to do what.

The other comment that I will make on that same point is, you know, a theme throughout this report is we need to develop or revise a set of regulations that we have so while it looks like the office is being asked to do a lot with respect to regulation, if the regulations are revised, all of that is done during that revision process so it may not be as burdensome as it appears when you read in each one NORE should issue regulation.

DR. MESLIN: Steve?

MR. HOLTZMAN: Well, first, a question. Do the people in the audience have access to the report that we are talking about? They do. Okay. So when we are talking about NORE they know what we are talking about.

PROFESSOR BACKLAR: It does not mean "no."

MR. HOLTZMAN: Okay. I was just doing a listening check when I went through my statements. I was not suggesting we should change from what is recommended here, the standard of minimal risk. I agree with you. Okay. I think it is consistent with

what we have done before. The implication of it is -- because what is the implication of minimal risk versus nonminimal risk?

It is precisely what Bernie has indicated and I do take us to be saying just because a population is in a -- a population in its nature has a more risky existence, that does not mean you should then just get -- go by with the administrative review. It is more than minimal risk, subjected to full IRB review. In that review one could say given the nature of this population, it is not that much more risky and the benefits outweigh the potential harms.

So it is -- so I am in complete agreement with the way we have written it. I just want -- so, Harold, when you raised the question about the profound implications of that definition, I think that is part of what you were driving at. Are we still in concurrence with it and I think I certainly am.

DR. SHAPIRO: Well, I certainly am also. I am still a little uncertain as to where we stand with a little different dimension with the vulnerable population. We are talking about these people, the examples we have been using are people who are already very sick, it means you can pile more risk on them. Of course, I agree with what everyone has said on that issue. I take that as an issue that is

behind us.

There are other -- there is another dimension of that, another facet of that. That is risks which are every day for some populations and very difficult for other populations. That is there is another way of looking at that. Some things may be very difficult for children and every day risks for adults or an every day risk for healthy adults and really something of considerably more import for let's say people with certain mental disorders let's just say.

So there is another side of that and if you go down to this minimal risk recommendation where it takes up this issue because IRBs should determine whether the level of risk remains minimal, but that is already in the IRB. Right? That is before -- someone says that you are giving that -- if I understand this, Marjorie, you are giving that determination to the IRB, which eliminates the possibility in those cases that it is going to be administrative review.

I am just not sure exactly how to parse these out because there is two different sides to that issue. I completely agree where we are in the beginning of this recommendation. I just would like, and I do not have some language now, to think through what it means for risks that are high for some populations although minimal for the general

population. There may not be enough of those but I just want to be clarified in my own mind how to deal with this.

DR. SPEERS: Let me just jump in and clarify at least what the intention was here and maybe the intention was correct although the words are not the best words.

This particular sentence was added to this recommendation based on our discussion at the last meeting where we -- what we discussed was a determination that a study is minimal risk could be made based on the assumption that the people participating in that study were from the general population. They did not have any vulnerabilities.

But we also acknowledged that if the study would involve individuals who are vulnerable then that determination of minimal risk may not hold because it is based on what is minimal risk for the general population and not for the vulnerable population so an IRB should not then just blindly move forward but needs to recalculate whether it is minimal risk given that vulnerable individuals are involved. That is the point we were trying to make here so I can tell we need to make that one clearer.

Now there is another issue that I am hearing around the table that I want to be clear on and that is if a study -- if a study involves individuals who are vulnerable and it is a minimal risk study, it is

still a minimal risk study, does -- is that type of study eligible for an administrative IRB review or does it go to the full board for review?

Now what we are saying in this report -- I will tell you what we are saying in this report. We are saying that studies that involve minimal risk, if it is determined that they involve minimal risk and they involve individuals with vulnerability, those studies could be eligible for administrative IRB review. So if that is not the sentiment of the group then we need -- we will need to change that.

DR. MESLIN: Alex?

PROFESSOR CAPRON: My sense is that the question of administrative review is the crucial issue here and the problem that we face is that when an application comes in, the researcher will have been asked to characterize the research and say does this involve more than minimal risk and; if the answer to that is no, are you applying for administrative review, yes; does involve vulnerable population, no.

Now that then puts it in the hands of the administrative officer of the IRB the responsibility that Bernie was describing a moment ago, which is understanding enough about what is really involved here to be able to say, wait, that initial characterization is or is not right.

And I gather that we think that that will

not be a problem because what we are thinking of, and you can correct me if I am wrong, is that this NORE and other processes, but particularly the NORE is going to give us a long list of illustrative interventions that are regarded as minimal risk and others that are regarded as more than minimal risk.

And so it will be in some ways a bureaucratic undertaking to say is it from column A or column B, and judgment will be only exercised as to something that is quite novel.

What we are saying here is then the further judgment that if you are using this intervention with a group will also -- that might -- that has been characterized by the researcher as not a vulnerable group but which someone else might say, wait a second, there is something vulnerable, is that equally an administrative decision.

And the problem is if we say no then we have basically removed administrative review because unless you are just gathering an average population off the street again of healthy individuals, so-called normal volunteers or something, there is always a possibility that someone with some sophistication in a particular area of medicine or other area of science will look at that and say, well, actually in this -- some of the people who you are describing, children, people with this or that disease actually are slightly more vulnerable because

of an interaction which is unusual for them with this particular intervention. And we would not regard it as the same level of risk for them.

That kind of sophistication is not the kind of bureaucratic judgment that we thought checking off whether or not this really is in the minimal risk category, but if it is not then basically every protocol that does not just have a cross section of the population will have to be reviewed by the full IRB.

Conversely, if we do not say that, if we say, well, it is only when the researcher identifies that there is a vulnerable population, and then obviously it would have to go to the IRB for this second step evaluation of whether it is equally vulnerable -- equally risky for them or more risky, we are really putting up a huge incentive to people to basically always claim their research involves no vulnerable populations except when they could not in a straight face do that. I mean, if they have got cancer patients who are very, very sick, they are not going to be able to say that is an average population. But short of that it is always -- the incentive goes that way.

I think we have ourselves a real dilemma here and I am very disinclined to treat this judgment as the same as the judgment about minimal risk which can be kind of do you fit in one of the recognized

examples of this is just a standard intervention and does not involve much risk.

DR. MESLIN: Steve, and then Bernie, and then Trish and Arturo.

Steve?

MR. HOLTZMAN: You are absolutely right, Alex. What do we want of this administrative review? And it is because who decides even the beginning of whether an administrative review is necessary. Am I dealing with human subjects research or not?

So I actually go -- I am not sure where you went with it but I think I would go in the opposite direction and I look at this holistically. And I say we are recommending an overall system in which investigators are certified, IRBs are accredited, and we are going to -- what we are postulating is a community of researchers and those who review research who are much more sensitized to these issues and much more educated about them, right, and which an investigator would be doing an analysis such as the analysis we have on page 54 of chapter 3 about examples of types of vulnerability and educated to do that, right.

So I can see it is more than just a check the boxes of the vulnerable but do you -- is it a vulnerable population; I believe it is not a vulnerable population. You have a grid like this and this is why it is not.

So I guess where I would want to come is we are setting up a -- we set up the system that assumes all of the system is working.

DR. MESLIN: We have Bernie.

DR. LO: I agree with Steve's point that we have to envision just working in a system where educators, IRBs and IRB administrators are better trained than they are today.

I would also like to put in a plea for having some flexibility and trying not to sort of do everything. I mean, the way I imagine this in my institution is it goes to two administrators who do this full-time, who are really good at this, and who are really very willing to pick up the phone and call someone and say, "You know, I just got this protocol. There is something about it I am not quite sure about. Let me run it by you. What do you think?"

So that there is a whole gamut of things that administrative review can encompass, including getting the kind of expertise that Alex rightly pointed out may be necessary with some protocol. They can always, it seems to me, be referred on for full IRB review.

We need to specify a little more what this administrative review is, I think to sort of call attention to Alex's point that we do not mean it to be something a computer can do. Just sort of matching do you have the key words here. There has

got to be some judgment and discretion.

Let me go back to Steve's point that we really want to turn this over to people who are trained and then trust to their discretion but hold the IRB as a whole and the investigator responsible if things go wrong.

But I do not want to sort of have us trying to micromanage the details so, you know, it can never go -- it has to go to full IRB. Let the individual IRB work that out and, you know, put enough of the surrounding structure in place to make -- give us confidence that it will work.

DR. MESLIN: Trish?

PROFESSOR BACKLAR: It is actually very difficult to do this right. I have a lot of concerns and I think, Alex, you laid it out and all of the different possibilities that could go right or wrong.

I am trying to think of how one could put this in a way where one would have -- I know you are talking about, Steve and Bernie, that you are going to have these checks and balances, people are going to know what they are doing and so on and so forth but they are human.

And researchers have had plenty of time to prove how much they know about protecting human subjects. We have a long history of problems where we allowed researchers to do pretty much what they wanted and maybe just because they are trained it

does not mean that they are still going to protect people adequately.

One of the things that we did in the Capacity Report, which was really quite important, is to make sure that when you had certain populations who might have certain vulnerabilities that you always had somebody on the IRB who could represent the interests from that community, whether they be advocates, the members of the population themselves, their families or whatever.

And, yes, and I am sure that the administrators at UCSF are very good and very careful, but still I worry that if we do this without some kind of other -- maybe in the text, maybe in the recommendation itself, that one would want to have some protection for certain kinds of populations. Whether it is going -- you know, saying that you would go back and get some consultation with members of the community of that particular population.

DR. MESLIN: Arturo?

DR. BRITO: Trish, I agree with your concerns but I have to go back to what Bernie and Steve were saying. I think at some point, in essence, we have to have some faith in this process and the administrators and I also thought about that, too. At UCSF, sure, you have somebody that is very well trained and very thoughtful and a very good administrator but I think we also have to have some

faith here in what we are proposing in the certification process.

My concern is that we are going to go -- once again we are falling in the same trap about the protection of vulnerable populations to the extreme of exclusion where we are going to end up excluding vulnerable populations. I go back to the rephrasing of the sentence but I will not get into that again. But I think we have to be very careful because even in our analytical model of vulnerability described later in the chapter that we talk about specific situations that places people vulnerable -- as a vulnerable group. We may exclude a vulnerable population from studies that really are minimal risk even for that group the way this regulation is written as it is now.

So I would be very careful and I think sometimes even vulnerable people have a right to participate in research. That is minimal risk or greater than minimal risk if they choose to do so and I think those studies that are minimal risk, even if you are vulnerable but not to that specific study or protocol, then it should be allowed to go through administrative process as anyone else would.

DR. MESLIN: Alex?

PROFESSOR CAPRON: I understand the concern, Arturo, but I do not read the recommendation as involving that. It does not say that the research

cannot go forward. It says simply that it gets a little more scrutiny than it would from an administrator. And if as a result of that scrutiny people say, wait a second, we are dealing with something where a description of this as minimal risk for the other consequences of that division as to the other parts of the process -- for example, if it is children and it is more than minimal risk we may run into some questions about it being allowed only when the benefits of that intervention are greater.

I think that that is appropriate. I mean, you would not want a situation in which the only way it could be done is slipping by through an administrator who was less acute than Bernie's administrator and did not recognize it. We are not talking about something which is a barrier to their participation. We are talking about something that is an extra requirement for scrutiny. The outcome of which is not necessarily negative to their involvement.

It has the kind of sensitivities that Trish described. We have said if it is a vulnerable population with certain mentalist abilities the board that reviews it should have some representative of that group who will be aware of special issues that may arise in the intervention for that group that would not arise with others.

DR. BRITO: May I respond to that? I think

the barrier is going to come from the fact that when you have studies where you have an IRB or people submitting protocols to the IRBs and they start seeing that, wait a minute, it takes longer to get this protocol approved because we are involving vulnerable people in a study that is minimal risk even for this group and the administrator interprets this -- they -- this has to go through a full protocol IRB, it becomes more burdensome for the investigators. What is going to start happening is people are going to be excluded from these studies that maybe should not be excluded.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: So one thing I think we should all make sure as we discuss this that we look at page 57, which is where the rubber hits the road with what we are saying, right. And, also, reflect on the fact that in the current system specific populations were defined as vulnerable and, as such, by definition, they had to have a full IRB -- the full IRB review.

You are shaking your head no.

Well, let me make -- I think one of the things we are recommending here is do not think about a vulnerable population as some descriptor. Rather do an analysis to determine whether this group is vulnerable in this context. Right? And we all agree with that.

So you have already given to the investigators and the administrator review the key exercise in judgment when you think about it. So to Alex's point if you are going to give them any judgment, you either take that because the same point can be raised, right, you are saying you cannot trust the investigator and the administrator to determine whether it is minimal risk because it is a vulnerable population but we are trusting them to determine whether it is a vulnerable population. Why are we trusting them with that? Why are we trusting them with determining whether they are dealing with human subjects research at all? You will drive it all the way back if you are going to be consistent and I would think that it is unworkable.

DR. BRITO: Are we in disagreement?

MR. HOLTZMAN: No, you and I are not. I am in disagreement with Trish and I think maybe Alex but I am not sure.

DR. SHAPIRO: There obviously is an issue here whether you can ever have administrative review for the population which somehow is determined one way or another to be vulnerable or whether -- or a population determined somehow to be vulnerable. You always want to go to the full IRB review and that is the kernel of the disagreement here if I understand the discussion.

And without trying to -- we are not voting

on this now because this has got to be rewritten and so on, and there are other issues that have come up, how do people feel about -- that is a very important question. And it would be hard to rewrite this recommendation if we did not have some sense of where people stood on this issue.

How many of you feel that at least under certain circumstance -- there are circumstances where even dealing with a population determined to be vulnerable you could be eligible for administrative review as defined in this gestalt.

(Show of hands.)

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: So let me -- Alta. I am trying to understand where Alta is.

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Hand up. So are you asking a question or is your hand up?

PROFESSOR BACKLAR: My hand is up.

DR. SHAPIRO: So you think it should be eligible or should not.

DR. BRITO: Should be.

DR. SHAPIRO: Should be, yes.

PROFESSOR BACKLAR: Oh, I think it should be eligible in many situations for administrative review.

DR. SHAPIRO: All right.

PROFESSOR BACKLAR: Absolutely. Social

services research, for instance.

DR. SHAPIRO: All right. You have at least some initial sense. We are going to have to struggle with this. We are going to have to come back to this again as we articulate the recommendation further.

Marjorie, do you want to -- let's move on a bit and see if we can get to a few more of these?

Yes?

DR. MIIKE: What are we going to do about your initial question about that one sentence in there because it is -- we are just going to eliminate that?

DR. SHAPIRO: I think that has got to -- we have got to rewrite this. I think that sentence is still a problem.

Marjorie?

DR. LO: I would like to raise a point that sort of reads through all these recommendations and it goes back to a comment someone made earlier about all these recommendations being phrased in terms of NORE is going to do this and do that. You know, when I come away from this, NORE is this huge new entity that is going to do this, this, this and that. And I think a lot of people are going to be very concerned that we are creating sort of a bureaucratic behemoth and a lot of this does not have to be done by NORE. I think it does not have to take the kind of regulatory aspect that we are writing in. I mean, it

is issuing regulations in most of these recommendations. I think a lot of what it should be doing is more issuing guidance, stimulating deliberation.

There just was an example this past couple of weeks with Greg Koski's new office running into a brick wall where they tried to impose standards of educating investigators. Everyone thinks it is a great idea but the way they did it was viewed as heavy handed, obtrusive, counterproductive, and we just raise hackles of people saying there go those people again issuing regulations, red tape, and not really helping with the substantive problems.

I really would suggest that we try and rewrite this, both to define better what NORE is going to do and to really address concerns that we are creating a bureaucratic monster because I think that is going to be a reaction that many people will have from congenital philosophy but good scientists are going to think that, too, based on their experience.

DR. MESLIN: Alex and then Jim?

PROFESSOR CAPRON: Well, I really want to nip that in the bud.

(Laughter.)

PROFESSOR CAPRON: It seems to me that what we are describing in this office with this somewhat awkward name is simply whatever the federal lead

agency is has a responsibility for the regulations. And we are not talking about anything that is more or less bureaucratic than present arrangements or than previous arrangements. We are not talking about anything that I think has to issue regulations as its only way of communicating.

If Bernie's point is that we ought to be careful in describing which points are appropriate for regulation and which for guidance, I agree, but the fact that an office has a new name -- what we are talking about here is the fact -- I think we all recognize that 45 CFR or the Common Rule is now up for grabs. I mean, the time has come and which we are contributor to a process of some reformulation of the substantive standards and the procedures under which those standards are applied.

And now I just hate to have coming out of this Commission any suggestion that we are creating a behemoth or any other strange animal. We are just talking about a normal process now lodged in an agency which will have the ability to speak to all federally funded and privately funded research but it does not become bureaucratic because of it. Its role vis-a-vis that research is not necessarily dramatically different than what it would be if it were OHRP or OPRR or any other OO.

DR. MESLIN: Jim?

DR. CHILDRESS: Alex's point is well taken

in that regard and yet let me affirm with Bernie that there is some risk in having proposals regarding regulations and guidance tied to an organization that does not exist and may never exist. And if we -- I want to go back through the report and make sure that we are clear and I have to go back to the very beginning and see that at each point where we say this that we are not simply tying the faith of what we are doing in terms of the public perception to an organization that again may never come into existence and this may simply be a matter of checking our wording throughout.

DR. DUMAS: I am trying to catch up. Did we finish with this issue of minimal risk and vulnerable populations because I am kind of --

DR. SHAPIRO: Oh, yes. Finish is too strong a word. But, yes, we want to go on to other aspects of chapter 3 before we -- just because the clock is --

DR. DUMAS: Are you going to come back to this ever?

DR. SHAPIRO: Oh, yes. Sure.

DR. DUMAS: Okay.

DR. MESLIN: Alex?

PROFESSOR CAPRON: On the point that -- I mean, Jim, one way of dealing with that is to make -- put all the recommendations in the passive voice, regulations or guidance as the case may be should

make clear that...the alternative is to say NORE throughout and then at the beginning of the report and at other appropriate places say if NORE does not come into existence then OHRP and the interagency task force should ensure that these steps are taken. Either way, generally things that are in the active voice rather than the passive are clear and easier to understand.

DR. SHAPIRO: I agree they are clear but they also presuppose an actor and I want to make sure the actor exists and so I think we need to take the version that you suggested and at least go back to the beginning and make sure we have indicated that.

DR. MESLIN: Carol?

DR. GREIDER: I just want to concur strongly with what Jim said. I have also felt reading through the recommendations it was too heavy handed on repeating NORE every time and much as I would hate to suggest the passive voice as a writing style, if that is the only way to do it, I would certainly prefer that than having it repeated. I do not have a problem with proposing NORE up front and then have the rest sound more like guidance rather than a specific institute has to do something.

DR. MESLIN: Larry?

DR. MIIKE: You know, I raised this issue before but I think what we have to remind ourselves is that we are extending this -- let me back up a

second by saying that I would have preferred a model where we had some lead office with much of the implementation delegated to the agencies that funded research.

However, since we are including all research in the United States I did not think that such a model was possible because I do not know how you deal with the private sector.

I think we have gone back and forth about -- you know, I would rather have a more general statement rather than these specific kinds of things and I think Jim is right. We have got to find a way to really basically say a word -- everybody is talking about reforming the system. We agree with that. And the elements in the reformed system are the following. So I think we need to rethink about how we write these specific recommendations.

I understand the reason for why you say that, okay, Congress should pass this and the reconstituted office should do this, IRBs should do this. It is a much more concrete way of dealing with this and making people understand what their specific responsibilities are but we have got to find some way to -- I agree with everybody else.

(Laughter.)

DR. MESLIN: Bernie?

DR. LO: If I could just follow on, it seems to me that the value of our report is not as an

action blueprint. It is a thinking blueprint. And what we have to offer are ideas on what the system ought to look like at the end, not specific ideas of should it be NORE, should it be Congress, should it be a rejuvenated OHRP.

I think the more we can sort of stay away from that level, which is going to get worked out far beyond our control, and stick to the substantive ideas -- I mean, earlier we were talking about really interesting ideas about a new way of thinking about risks and benefit, a new emphasis on minimal risk research, and that should be the substance of our report, not the sort of mechanism by which those get carried out.

DR. SHAPIRO: Okay. Why don't we see whether there are other aspects, Marjorie, of this particular set of recommendations you would like to take up now. We only have a short amount of time before our break and then we have to move on to other aspects of the report.

DR. SPEERS: Okay. In this chapter I want to make sure that we have time to spend on the recommendations related to vulnerable groups. However, let me ask quickly whether you have any comments on the recommendations related to informed consent or privacy and confidentiality.

Jim?

DR. CHILDRESS: On 3.4, I very much like the

direction of Alta's revision and I think that improves it stylistically while keeping the core of the substance so I would strongly recommend that.

And let me just make one other reference to a textual point. On page 28 and also on page 31, we refer to the required elements of consent. Now I know where this fits in the regulations. I know what the heading is. The basic elements of consent. But these are not consent elements. They are elements of disclosure and there is no way we can talk about consent as a statement that the study and description of words so I think just logically and conceptually we have to do that, whatever the heading is in the regulations.

DR. SPEERS: Any other comments on 3.4? If not on 3.4, I will incorporate Alta's language into the rewrite.

PROFESSOR CAPRON: Yes. I had a lot of rewrite of 3.4. I have not read Alta's. Certainly it needs to be rewritten and there may be a line to pick up from Larry Miike here that some of the things that are said here could be in the level of commentary more so than is usually the case.

DR. SPEERS: Bernie?

DR. LO: On this notion of informed consent, I would suggest we introduce the idea that we do not really know how to go about doing this and the guidance may be down the road after we have done some

research and found out more about how you effectively do this.

I mean, it sort of suggested here that if we sat down and thought about it, we would really know how to do disclosure in a way that maximizes autonomy and understanding. I am not sure we do. So I think stimulating research and discussion is something that NORE should be doing as well as issuing guidance and regulation.

PROFESSOR CAPRON: Could we get clarification on one thing because both the original and Alta's include the language. It says "information that is disclosed during the informed consent process should be tailored both to the type of research being proposed and the interests of the prospective participants." Could you say something more about what is intended by number two?

DR. SPEERS: Yes. There have been a few studies that have been done that have talked with prospective participants before a study asking them what it is they would like to know about the study before they participate in it, and sometimes what participants would like to know about the study are different or there are issues that are in addition to what the regulations, I am sorry, would require as elements of disclosure.

So we are saying -- what we are trying to say here is to include what participants want to know

and not have a completely paternalistic perspective.

PROFESSOR CAPRON: Right. Well, could we convey that by saying "and the informational needs or what is known about the informational needs of the prospective participants" because that is what that prior research would be designed to turn up?

DR. MESLIN: Bernie?

DR. LO: On 3.5, the second sentence, "takes into account local variation of what is considered adequate or appropriate." I would like to key not to what is usually done but what ought to be done taking into account local special considerations. I am not sure that is the right language but here it reads like we are sloppy in San Francisco, you know, NORE ought to recognize that.

DR. MESLIN: Arturo?

DR. BRITO: I had some comments not on that recommendation but the text leading to that. I thought there were some areas of concern there. Particularly where you are talking about the -- where people's first language is not English. The implication here is that sometimes -- the way I read this is sometimes people are included in research when English is not their first language even if the written informed consent document is not translated into that language. And my experience has been, is that what often happens is that if there is no one available to translate a written document, they just

exclude that population group from the research. So I think I can give you my notes here on that.

And also the reference to written forms are not the norm. It is the -- at the end of the second sentence in that, you know, top of the page of 33. It implies that in phone surveys, written forms are the norm, and that is not necessarily true.

There are just some things here that I have concerns. I will be glad to give a written recommendation. I think it relates to what goes on in recommendation 3.5 and I do not think we mean to say local variation as Bernie said so I will give that to you.

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: Arturo's comment actually triggered something that I had failed to mention in any of my previous e-mails and it transcends this particular recommendation but it links to the conversation earlier about how to ensure the inclusion in appropriate fashion of so-called vulnerable populations.

I do not think I remember in this report any place where we explicitly tackle what has been a perennial problem about the justice of -- or not just -- let me just take away the word "justice." The comprehensiveness of the participant population in studies.

You may recall there was a long struggle about the inclusion of fertile women in research studies and one of the reactions that IRBs had prior to the creation of some degree of federal policy on this point was that the role of the IRB was simply to ensure protection for those people who actually were being recruited and not to worry about whether in the end an appropriately broad population of people was represented in the research either in this particular study or in similar studies around the country such that you could ensure that the research results were generalizable to the entire population.

And Arturo's comment about the reaction being to simply exclude people who do not speak English because it is easier because you do not have to have a translator triggers in my mind the possibility that we might want to tackle that topic a little bit and I understand because we are sending this out for review that we are not in a position to write a recommendation right now. It is going to be very tricky.

But that we might want to invite reactions on that topic from the reviewers in preparation for beginning to think about it more seriously because the notion that the research ought to be generalizable to the whole population and, therefore, efforts have to be made to ensure that comprehensively includes men and women, people who

are European American as well as non-European American, people from different language groups, and people from different age groups, children and the elderly is something that is a constant source of struggle and is not easily dealt with at the level of the individual IRB, which is often only looking at one single study that is part of multicenter trials or one single -- only one single study that is part of a series of studies going on over years.

But it is an opportunity for us to say something about the role of research more generally and not only about the protection of the individual people who happen to be enrolled in a particular study.

DR. MESLIN: Trish, and then Larry.

PROFESSOR BACKLAR: Yes, actually this is a real problem and more often than not you will see as criteria for your subject recruitment and inclusion will be English speaking only and that is because it is very expensive. Researchers perceive, and sponsors and so on and so forth, so it is very important to address.

DR. MESLIN: Larry?

DR. MIIKE: Well, I do not see the harm in including a discussion of that in the report. I would object to any kind of recommendation on that. That seems to be way beyond our charge. That is -- you are really talking about what -- that should

really be addressed at the research funding agency and others and I think that is just stepping beyond our bounds.

DR. SHAPIRO: Any other comments or questions before we break on any series of recommendations? Bernie?

DR. LO: With regard to informed consent, one of the issues that came up in the testimony received from people who do sort of a variety of types of research is how in a lot of social science research where there is interview research or survey research the informed consent model that we have for clinical trials does not really work.

I am just wondering if in these recommendations we want to -- we sort of talk about waiving informed consent in 3.6 but the kind of detailed informed consent with formal consent form and signed written consent to do a questionnaire is just like overkill and I am just wondering if we should try and deal with that in some way as part of our drive to put the emphasis on where the risks really are.

Arguably if people can sort of just stop answering the questions, the amount of risk they are subject to is very different than if they are, you know, in a clinical trial that involves invasive procedures.

PROFESSOR CAPRON: Could I ask for

clarification on that, Bernie? What are you reading to require signed consent?

DR. LO: Well, do we want to say something in our recommendations to allow or encourage NORE or IRBs to develop procedures by which a modified consent process may be deemed appropriate for survey research or interview research?

PROFESSOR CAPRON: I thought that is what 3.5 does in part.

DR. LO: Well, 3.5 may do that. It does not -- I mean, I think it needs to be right into the 3.5 rather than saying explicitly we recognize certain types of social science research, the kind of full-blown consent form or two-page consent form but signed may not be appropriate.

PROFESSOR CAPRON: Well, what -- maybe Marjorie should say something about the intent. I read -- I do not like the second sentence in 3.5 partly for the reasons that you suggest. I mean that it encourages us to think local variation could mean simply some place is sloppy and can say that we just do not that.

But the notion of under 3.5 is simply an elaboration of what the present regulations allow, which is that you can have other means of documented consent than a signed consent form. Isn't that what it --

DR. SPEERS: I think both 3.4 and 3.5

addresses the issue that Bernie is raising in that 3.4 is saying the consent process should be appropriate to the type of research that is being done and 3.5 is dealing with documentation of that informed consent process.

DR. SHAPIRO: Okay. Other questions?

Jim?

DR. CHILDRESS: You are asking for the rest of the recommendations.

DR. SHAPIRO: Right.

DR. CHILDRESS: Regarding the privacy and confidentiality ones, I very much like Alta's proposed revisions 3.7 and 3.8. They meet Larry's criteria for being briefer. I think they also are much clearer and sharper. I would change them -- if you are looking at her sheet, 3.7, the second sentence I would change. "The guidance should also explain how research practices can threaten privacy and confidentiality and so forth." So I would urge that we consider her versions as preferable at this point.

And then I also share the concerns she has raised for the -- for 3.10 and following about -- and it has already been raised this morning, too, about what appears to be the reintroduction of the three tiers but at least I think we need -- the Commission needs to discuss that very carefully because, for instance, under 3.10(2)(b) got a high level of risk

as distinguished from minimal risk or presumably slightly greater than minimal risk then all of a sudden some other things kick in.

And we at least need to work through that and see whether we want to go to an approach that we rejected in the Capacity Report.

DR. SHAPIRO: Marjorie?

DR. SPEERS: I think that the recommendations related to vulnerability are so important that after the break we need to come back and pick them up and we can -- hopefully, maybe one of the other chapters will not take as much time so we can make up the time but this is a critical chapter.

DR. SHAPIRO: I agree we do.

PROFESSOR CAPRON: That is if we have more time.

DR. SHAPIRO: Yes. That is hopeful sign but perhaps not realized. But we do have to come back to this no matter what. I mean, if we get it today or we do it some other time, we really have to come back to it because they are critically important and I have the same set of concerns on 3.10 as those that Jim just articulated.

Well, why don't we take -- Steve, I would like to take a break now but if it is a short question let's deal with it.

MR. HOLTZMAN: It is not short.

DR. SHAPIRO: Not short. All right. Let's take a break for ten minutes. Let's reassemble at ten to.

(Whereupon, a break was taken.)

DR. SHAPIRO: Colleagues, I have looked over our agenda and the various recommendations, and although we are running behind our time table on the agenda, I really think there is one recommendation -- one of the recommendations in chapter 3, which we ought to look at specifically before going on. And that is recommendation 3.10. I think that is the last one in that chapter.

PROFESSOR CAPRON: There is one more.

DR. SHAPIRO: One more. 3.10 is the one I have that I want to focus some attention on.

Let me begin that part of the discussion just by turning to Marjorie to articulate what was trying to be accomplished in this because I think there are issues there that we need to resolve amongst ourselves about how we feel about it.

Marjorie?

3.10. Page 60. It is also on 66 in the summary.

DR. SPEERS: Okay.

DR. SHAPIRO: Marjorie?

DR. SPEERS: Yes. Okay. Here is what we are trying to say in recommendation 3.10: This recommendation is based on having conducted a

component analysis as was recommended in the earlier part of the chapter.

It is -- this recommendation is saying that when vulnerable individuals are involved in the research first that research involving no more than minimal risk may be eligible for administrative IRB review. Now this is based on the assumption that the judgment has been made knowing that there are vulnerable individuals involved that the study is still a minimal risk study and in that case it could receive administrative IRB review.

The second part of this recommendation starting under item 2 in it is saying that the classification of minimal risk should be used to limit exposure to research risks. And again remember that the discussion regarding the use or the utility of minimal risk was to do two things. One is as a sorting mechanism that is to sort research into that which can receive an administrative IRB review and that which is required to have a full IRB review. And the second use of minimal risk is to limit exposure of individuals to research risks.

For this function of minimal risk we are saying that it is only applicable to the components that are designed solely to answer the research questions. It would not apply to those components that in addition to answering the research question they also provide the prospect of benefit. And just

to refresh you, the reason for that is because those components that offer the prospect of a direct benefit are justified based on equipoise.

So if you can just -- just to go through the recommendation, therefore when components that are designed solely to answer the research question involve more than minimal risk and when the research involves persons with a capacity related cognitive vulnerability, so of all of the vulnerabilities that we discuss in this section, here we are only talking about those who have a capacity related cognitive vulnerability. And those individuals are clearly unable to give informed consent. We are saying such that research may be permitted only if the potential knowledge benefits are important enough to justify the exposure.

We are saying that in order for the IRB to make that decision the IRB should seek public and expert input into making that decision. So an IRB cannot just make it alone. They would have to seek the additional input.

DR. SHAPIRO: Could I just ask a clarifying question on 2A, which you just discussed?

Am I correct to say that it is really only the latter that is new here? Everything else is just as before. It is just the latter requirement, the case of this population as I understand what you are saying.

DR. SPEERS: That is correct.

DR. SHAPIRO: Everything else is just repeating in different words what we have already said.

DR. SPEERS: Yes. The first part of that recommendation is describing the circumstances that we are talking about and then it is the last sentence that adds a new requirement.

DR. SHAPIRO: Thank you.

DR. MESLIN: Larry?

DR. MIIKE: I guess I have a different kind of problem with this. It says the recommendation is about minimal risk but what you have described so far is just the usual way one would review a research study. So I do not see why -- it seems like this goes way beyond what the recommendation says it is about. You understand what I am saying?

What I am saying is that when it is not minimal risk what you are describing is the usual way one would go about evaluating the risks and benefits of the study. So I do not see why we need to reiterate that. I think that is part of the confusion that is going on over here.

Anyway, that is what is confusing me about why it is written like this.

DR. SPEERS: I think you are correct that the IRB would do what it normally does. The issue here is that we are speaking about individuals who

are unable to give informed consent and how to handle the IRB review for that particular group of individuals. What this says correctly -- what you said it is -- is that it says that the IRB does what it normally does with the one additional requirement that input needs to be sought.

PROFESSOR CHARO: Hand up.

DR. SPEERS: Just let me -- what I would like to do if I could is just finish and then open it up for discussion.

It goes on to further say that for those same components that involve more than minimal risk but involve a high level of risk that additional review and oversight should be required by a national review panel.

And then it further says that for the other types of vulnerability meaning those where individuals are capable of giving informed consent but they may still have a vulnerability for another reason, the classification of minimal risk should not be used to limit exposure to the research.

So what we are saying is, is it is for those individuals who have a cognitive capacity vulnerability where they are clearly able -- unable to give informed consent that we are addressing here in (2)(a) and (2)(b).

DR. MESLIN: We have Alta and Rhetaugh.

PROFESSOR CHARO: Eric, was that an

invitation to speak?

DR. MESLIN: Yes, Alta.

PROFESSOR CHARO: Sorry. Every once in a while it is a little hard to hear.

Regarding 3.10(2), as mentioned on the e-mail, I would like to register a strenuous objection. It is true that it is written -- it is simply as additional protections to what is currently in the regulation that now exists.

However, the Capacity Report made a series of recommendations for protections that go beyond the current regulation. This section retreats from the protections that we recommended in the Capacity Report. Specifically, this recommendation suggests that the more than minimal risk components that offer no prospect of benefit to the individual, that the IRB can approve that here with public input; in the Capacity Report only with the assistance of a national panel.

I prefer the Capacity Report's approach. I also as a general matter think it would be very poor form for us to produce reports that have conflicting recommendations without specifically deciding that we are going to renounce the Capacity Report before putting new recommendations out there for people to consider.

Second, with regard to the reference to high level of risk in 3.10(2)(b), again I would suggest

that we do not know what this phrase means but what we are creating here is a three-tiered system of minimal risk, more than minimal risk, and high risk, and that it is very similar to the one that was suggested based on the children's regs during the Capacity Report debates that had a three-tiered system of minimal risk, minor increment over minimal risk, and then some other unnamed level of risk.

We rejected the three-tiered approach then because we found in our discussions that it did not add to clarity. Rather it simply added to confusion. And here we are offering yet another version of a three-tiered system but with even more confusion because it is adding yet more phraseology that goes undefined.

DR. MESLIN: Was that the end of your comment, Alta?

PROFESSOR CHARO: Yes, it was.

DR. MESLIN: Okay. Thanks very much.

Rhetaugh?

DR. DUMAS: I want to join Alta in objections to this particular section. I am particularly concerned about the statement under 3.10(2)(a) that allows research on people with capacity related cognitive vulnerability even if it is more than minimal risk provided that the potential knowledge benefits are important enough to justify the exposure.

And I believe that this is contrary, as I recall, to the position that we took in the Capacity Report. So for that reason I am unhappy with that.

And, also, I agree that we should not now go to a three-tiered system of evaluating risk.

DR. MESLIN: Thanks, Rhetaugh.

And for the public who are out there, there may be still a number of copies of the Capacity Report that you have heard mentioned out on the table in case you are wondering about those.

Alex?

PROFESSOR CAPRON: Well, I assume that Marjorie's intention in putting this forward with the contradiction that it has to the recommendation in the Capacity Report was to leave it to the Florida Supreme Court to work it out.

(Laughter.)

PROFESSOR CAPRON: But I think that the only part of 3.10 that ought to survive is the first part which talks about the responsibility of the Office of Research Ethics, or whatever it is going to be, to provide the kind of guidance that will be necessary if the sentence in 3.2 that we were talking about before about the need to scrutinize protocols that are classified as minimal risk when they have vulnerable populations to make sure that it is still minimal risk is to be implemented successfully.

And I wanted to comment on that because I

have actually been convinced by the discussion and the points made by Bernie and Arturo and Steve -- so if I was wavering or unclear before, Steve, it was because I saw a dilemma and you have convinced me on your side but with the following caveat:

I think a credentialling system is an important part of the changes that we are talking about but it seems to me that whether it is as a part of 3.10 or otherwise, one of the things that we need to suggest is that part of an accreditation system for IRBs will be to look at the performance of the people to whom this administrative oversight is given and there would be in an appropriate credentialling system a measurement of outcome.

And if a site visitor at a credentialling process for an IRB were to say that there had been a number of protocols put forward as minimal risk in examining them that some more than negligible number seemed to have been misclassified applying a deeper review to them that would be a signal that the IRB ought to either reinstruct its administrator and hire a new one or for a period of time engage in the more meticulous examination of those protocols because somehow the process that we were counting on of this being a credentialed IRB administrator was not leading to the results and was leading to the very problem that caused me, Steve, to feel a dilemma in the first place.

And I am not satisfied with a credentialling process alone. I think we need an accreditation process that looks at outcomes and not just paper qualifications. And I would tie the two together and I do not know that that is part of the recommendation but part of the description of what this guidance should be that part of the implementation is in the process of looking at performance you see whether or not the guidance has been followed.

DR. SHAPIRO: Are the other comments on this? I think there is -- I am sorry. Let me see if there are other comments.

Let me go back and make sure I understand what is here once again because I am not sure. First of all, I want to say that I very much support what I take to be the spirit of Alex's observation regarding review of some kind, ongoing review whether accomplished through accreditation, audit or any other procedure that seems convincing to us. I really think that is critical for what we are recommending here. A critical component of what we are recommending here.

But the issue which Commissioners have spoken and addressed is -- or at least a number of you address an unwillingness to leave with the local IRB studies that are referred to here that are more than minimal risk. Plus an uncomfort or at least a discomfort with the so-called reintroduction of the

three categories of risk.

Now all I have heard so far are negative comments about that. That is you do not like it. We can accept that. I just want to make sure if people feel otherwise.

PROFESSOR CAPRON: Mr. Chairman, aren't there two things here at work? One is the notion of a minimal risk -- some undefined middle category of greater and then some -- but the notion that things which are greater than minimal risk, just the dichotomy between minimal and greater than minimal, and which do not involve a competent -- do not involve direct benefit and do not involve competent informed consent, a prior advance directive and an agreement by the legally authorized representative.

That if they do not involve either of those that they would go to -- under the Capacity Report -- some higher review.

And I thought you were suggesting that there was any disagreement with the higher review function. It is only --

DR. SHAPIRO: No.

PROFESSOR CAPRON: I am sorry. It is only separating it out as to --

DR. SHAPIRO: That is right.

PROFESSOR CAPRON: -- this defined category.

DR. SHAPIRO: That is right. If I misstated

it, I apologize, but that is what I intended. But I have not heard from the Commission. I mean, the Commission seems agreed on that. I mean, unless I hear other voices, we will just go on and rewrite this as appropriate.

Steve?

MR. HOLTZMAN: So I will register my disagreement but it is for the same reasons I disagreed during the Capacity Report but it does not make sense to me to ask the Commission to go back and rewrite the Capacity Report in this context.

DR. SHAPIRO: Bernie?

DR. LO: For the record, I disagreed then and I disagree now but I lost that battle then I think I am losing it now.

DR. SHAPIRO: And you do not want to reengage it at this time.

DR. LO: No.

DR. SHAPIRO: Larry?

DR. MIIKE: In the Capacity Report it says research could be approved by a higher level panel.

DR. SHAPIRO: Yes.

DR. MIIKE: Are we going to address that? Are we going to -- because people are objecting to a three-tiered approach here. What are we going to do with it?

DR. SHAPIRO: I presume from what I am hearing that the wish of most members of the

Commission is we address it in an analogous way, namely these studies would have to go to a national panel. Maybe NORE or some other panel. I have not thought that through.

DR. MIIKE: Okay.

DR. SHAPIRO: Carol?

DR. GREIDER: Can't we just point directly to the Capacity Report?

DR. SHAPIRO: Yes, we could.

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Hand up from Wisconsin.

PROFESSOR CHARO: Snowy Wisconsin.

I would also note that the Capacity Report did specifically say that a national panel could eventually return this kind of discretion back to the IRBs after having worked through some of the specifics about the kinds of interventions and the levels of risk and the scientific necessity, and that I see no reason that we should back away from that either.

Finally, that we probably want to cross reference the fact that earlier in chapter 3 we suggested that there be a better mechanism for regional and national panels to be convened for situations that require special consideration, only strengthening the Capacity Report's request that national panels be a real and not illusory remedy to this dilemma.

DR. SHAPIRO: Yes, Marjorie.

Thank you, Alta.

DR. SPEERS: Let me just ask a question to make sure we understand this in light of the component analysis that we have suggested.

If a research study involves both -- it involves components that are surely designed to answer the research question and it involves components that in addition to answering the research question, they offer the prospect of direct benefit.

Those studies -- as I understand it, in the Capacity Report those studies can be approved by the local IRB as long as they have a component that offers the prospect of direct benefit and we could say the same thing here. So we are -- what we might be talking about because again since in this report we are dealing with all types of research, if a research study, and it is any type of a research study, only involves let's say a component designed to answer the research question. So it is a survey. It is a medical records review type of study.

In those studies if those studies involved more than minimal risk you would want those to go to the national panel for review.

MR. HOLTZMAN: In this population.

DR. SPEERS: In this particular -- that is what I want --

DR. CHILDRESS: With all the conditions that

Alex said earlier --

PROFESSOR CAPRON: Not if they can have consented competently or if they have gone through the process of an advanced directive and their LAR approves. It was only when neither of those existed that we said it would have to go and then we went on and described, as Alta said, a process of sort of group learning on these subjects where eventually some types of studies might be found to be suitable for local review and this is exactly the kind of process which a nonbureaucratic/nonbehemoth NOR might help to facilitate.

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: On November 16th I sent an e-mail, although I do not recall any reactions to it, that actually set forth a kind of model situation for people to consider on exactly this point. And it suggested that we might have the following situation: A protocol proposed to test two standard therapeutic drug interventions on a cognitively impaired population over a period of months. The regime requires biweekly lumbar punctures to measure neurotransmitter levels in the spinal fluid.

These neurotransmitter levels will not be used to adjust the drug dosages or in any way provide any benefit to the participants but are merely being used to develop general data that might prove useful

in the future for understanding the effect of these drugs on neurotransmitters.

And the question then said what would be the implications of analyzing this with our Capacity Report's recommendations as the operating standard if we did it on a component by component basis?

And the answer is if you think a lumbar puncture is more than minimal risk or repeated punctures are more than minimal risk then it would suggest that for a cognitively impaired population that has not perspectively authorized this kind of thing that those punctures could not be done even though there are two standard therapeutic drug interventions being used on this population.

And I am personally comfortable with that outcome because I truly expect that if anybody does adopt the capacity recommendations, they will do it only if they create truly functioning regional and national panels so that this thing can work efficiently.

But I think that is an example of a situation where we can test our willingness to live by the Capacity Report's standards in a component by component regime.

DR. SHAPIRO: Thank you.

Trish, Bernie?

PROFESSOR BACKLAR: I want to ask Marjorie something, and that is you gave us an example which

was simply looking at medical records or a survey, which is very different from the possibility of having a lumbar puncture. And you said that this kind of research that simply looked at medical records and surveys that was going to this population would have to go according to this to a national review. Is that -- did I misunderstand you?

DR. SPEERS: No, you did not misunderstand me and that is -- and that is the reason to bring those examples out.

DR. SHAPIRO: If it is more than minimal risk.

DR. SPEERS: If those are more than minimal risk.

PROFESSOR BACKLAR: And you would characterize in that more than minimal risk something to do with privacy and confidentiality if it was simply medical records and surveys.

DR. SPEERS: The risks are likely to lie in those areas.

DR. SHAPIRO: Bernie, Steve, and then Alex.

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: What is that?

PROFESSOR CHARO: Hand up at the end of your list, please.

DR. SHAPIRO: Okay. Bernie, Steve, Alta.

DR. LO: I think, Marjorie, your example leads us to another issue, which is medical records

research or health services research and whether the rejuvenated oversight scheme needs to look at those differently than clinical research, which is not now the case.

In the HBM report, the Human Biologics Material Report, we took the approach of saying let's have a presumption that this type of research on stored tissue presumptively is minimal risk provided that...da, da, da.

And I would sort of argue the way out of the dilemma of having medical records research on a population that includes people who have lost decision making capacity, rather than sending it off to a national body, is to work with the presumption that that type of research generally is minimal risk provided that strong measures are taken to protect the confidentiality. Because it seems to me as you look at that type of research, the key issue is the main risk is from breaches of confidentiality. And if that is very strongly protected, it seems to me the risks could well be presumed to be minimal and then informed consent, it seems to me, is -- whether or not the patient lacks decision making capacity -- is not the crucial ethical issue in that type of research.

So I guess I am looking for a recommendation somewhere in here that addresses research on existing data trying to move it into a presumptive category of

being minimal risk research and, therefore, enjoying a less burdensome review process than is now currently the case often.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Well, Bernie and I were talking about this particular issue over the break, and I think it is a more general issue than -- in this particular recommendation than really would come up in the context of 3.6 and 2.3. So I want to bracket that for the moment.

But coming back to what Trish said, and Marjorie's example, if we go back to the discussion during the Capacity Report there were a number of examples raised of the kinds of studies -- the other one we used was a genetic study -- where people might feel that it is more than minimal risk and yet your intuition says this is not what we are -- we are trying to protect against the lumbar punctures. We are not trying to protect against that. Okay.

But it was a consequence we came and had to live with when we refused to try to go, for good or bad reasons, when we refused to go with the three-tier system of something of minor increment above.

So I think Bernie is right generalizing. It is a class of research which is essentially -- I am going to call it noninterventional that can take place on such a population. We either create a presumption that it is not minimal risk or we try to

treat it very, very differently in general.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: Yes. I strongly endorse Bernie's approach and what I think I understood from Steve, which is that it is entirely appropriate for us to expand on the HBM report here specifically and to say that the kinds of things that we recommended there that we create a presumption of minimal risk should probably be applied to medical records as well, and in that way clear out what I think of as being a diversion from a central point that I do not want to have lost which is the heightened degree of protection for the cognitively impaired that goes beyond what the IRBs are currently offering.

DR. SHAPIRO: Thank you.

Other comments on this?

These have been very helpful comments and I really appreciate it.

Any other comments on this?

Okay. I am sorry, Trish. I apologize.

PROFESSOR BACKLAR: I just want to remind us that we did get into considerable trouble in the Capacity Report with researchers who were social -- doing social science research and we tried to ameliorate it in certain ways but maybe not enough. And I think that we really do need to address that.

DR. SHAPIRO: Thank you.

Other comments?

Are there any other comments? We have really only about 25 minutes until we break for lunch but are there any other comments on 3 right now that you feel are important? We might as well take them and we may not get to 4 until afterwards.

Bette, and then Steve?

MS. KRAMER: I would like to back up. I did not realize we were going to leave issues of informed consent so quickly.

DR. SHAPIRO: Okay.

MS. KRAMER: You know, we are always looking for examples. I have an example, a very real life example that is going on in Richmond right now, and as I read through this material I do not know how it would play out in light of these recommendations that we are proposing.

The Medical College of Virginia, VCU, is one of the largest sites, international sites of twin research, genetic research on twins. And the problems that VCU has had last year with OHRR, they were -- their research was all closed down, including the twin studies, and they typically -- and, as I understand, this is typical of this sort of research all over, they do their research by telephone, which is to say they call the twins, they ask the twins for permission to call members of the family, they ask the twins to notify members of the family that they are going to be calling them, sometimes they do,

sometimes they do not, but nonetheless they do their research over the telephone by calling these people.

They have now been told that they cannot continue to do that, that the only way they can do it is by first getting a written informed consent from all of the people that they would like to call, which is a large, large number. And, of course, it is totally unrealistic to think if they send these informed consent forms out and ask people to fill them out and sign them and send them back in that they are going to get any kind of response at all, which means effectively the research is going to be stopped and has been stopped.

Now it seems to me, I am sure that all of us -- we get calls from telemarketers every day and there is a very, very effective mean way of letting them know you do not want to participate, you hang up and that is done.

So I do not -- I am having trouble understanding within these recommendations that we are making how is their particular problem going to be addressed. Is it going to be addressed? I do not know that you can call that a -- I mean, Marjorie, would this fall in -- it does not seem to me it falls in survey research. I am not sure it really falls in -- does it fall in survey research? Can you explain this for me?

DR. SPEERS: Well, I do not know if I can

explain it to you. The issue that you are bringing up and the particular case that you are bringing up could be addressed in one and two ways in our recommendation. One is when we look at chapter 2 and we look at the way that we have defined a participant in research, it could fall under who is a participant in research and who is not.

It relates to these recommendations on informed consent, the process and the documentation of consent in that what we have said in our recommendations here is that the documentation of the informed consent process -- that there should be documentation but that documentation should be appropriate for whatever the type of research that is being proposed.

So, for example, in telephone surveys a signed written consent form is generally not the form of documentation that is used. There might be other forms of documentation that can be the interviewer noting that the person has given informed consent, having the script there for others to look at, sometimes even some audio taping might be done just of the informed consent process, or there are other methods that are used.

With any set of regulations or guidance, the local IRB or an oversight office is going to interpret those regulations and without knowing specifically what is going -- you know, the specifics

of the VCU case, it can be a matter of a very strict or over interpretation of regulation.

MS. KRAMER: Well, actually I think what happened is that when they were closed down, all of this was closed down, but there are -- there have been no provisions for them to reopen it. What they typically do, as I understand, I have not been present when they have done it but this is what I am told, is that they call up those people of whom they want to ask questions, they tell them who they are, why they are calling, that they are going to be asking questions, which will pertain to certain subjects, and they solicit their permission to go forward with the questions. So they have the opportunity at that time to say yes or no. Or if they say yes and they proceed and they become uncomfortable with it they say, sorry, I am not interested in talking to you anymore and that effectively ends it.

I do not -- my question really of the Commission at this time is within these recommendations that we are proposing is there room for research of this sort to go forward without them -- without them having to go through an inappropriate consent procedure?

DR. SPEERS: I think Alex may answer but the simple answer is yes.

PROFESSOR CAPRON: Yes.

(Laughter.)

DR. SHAPIRO: Do you have a complex answer?

PROFESSOR CAPRON: Obviously, that is the other alternative.

I think the importance of the interchange it seems to me is a reminder that unlike the telemarketer who simply says I am calling for X, Y, Z research and we would like to ask you some questions about...that an informed consent process has the elements that you described. It probably has some disclosure about who the sponsor is, an offer very typically to make the results available, some indication of what will happen in linkage of your response to your name. All of these would be elements of disclosure that would go with consent.

But with that there would be no reason why in that circumstance the documentation could not be any of the kinds of things Marjorie described. A tape recorded version, simply a notation in the record that the script had been gone through, an offer to answer any questions had been given, any questions had been answered, and the person then said, "I agree to participate and I can stop at any time I want," and go on with the question.

So I -- it seems to me, if anything, our report addresses that emphasizing that it is the process of getting consent rather than the form that is important, the paper form.

DR. SHAPIRO: Okay.

Steve? Steve, did you have a question?

MR. HOLTZMAN: Again, you said anything else on 3 and the point that Bernie was raising does affect 3.6. It takes you back into 2.3 and so maybe we want to take that all up together but it is a general approach of looking at -- for the moment, let me call it noninterventional research, typically tissue and records research, and asking whether the focus and locus of protections ought to be with respect to confidentiality as opposed to a focus on informed consent but that is a long discussion.

DR. SHAPIRO: Yes. We will have to come back and address the set of issues that surround that because I think it is extremely important and we have to come back and deal with it so that is on our agenda.

Bernie?

DR. LO: Yes. I just wanted to follow-up to the discussion between Marjorie and Alex. Yes, I agree there is nothing in our recommendations that would preclude an IRB from doing those things. I would actually like to go further and say that we recommend that IRBs do that and not think about asking for either a signed consent form. Or what we have to do actually is send the written consent -- send the consent disclosure form to the subject rather than just doing it all orally over the

telephone. And similarly for face-to-face interviewing I am not sure it is necessary to use the same consent process.

So rather than just saying there is nothing in our recommendation that precludes that, we should say this is how we think it should be subject to what Alex said about confidentiality and being able to stop and this sort of thing.

DR. SHAPIRO: Thank you.

Any other comments to point our attention to some aspects of the recommendations under 3?

Eric, do you have something on 3?

DR. MESLIN: I was only going to direct Commissioners to something Alex had already said and that relates to the Capacity Report's earlier recommendations about national panels and the like and I think Alta alluded to it as well. It was the authority that we were -- you had proposed that the national panel would have to promulgate guidelines that would permit IRBs to approve protocols, et cetera.

It is a description of what could occur and there would be no reason why you would not want to endorse that same recommendation in this report but that you could read recommendation 2(b) along with recommendation 12 from the Capacity Report ad that might provide a bit of relief to the difficulties you are experiencing in 3.10.

DR. SHAPIRO: Okay.

Bernie?

DR. LO: General comment on the chapter 3 recommendations. I suggested earlier that one of the things I imagine NORE doing is sort of convening interested parties, stimulating discussion, trying to facilitate the kind of exchange of ideas among different IRBs and IRBs and investigators and ethicists. I think that is different from what we now have in 3.11, which is really a sponsoring research on -- on research. I would like to us kind of put that out as a prime role for NORE to be doing, sort of to bring people together to sort of talk about ideas, think about them, analyze them and suggest guidance, discuss tough cases, all the things that really can provide sort of a national educational and deliberative forum.

I actually personally think that is one of the most valuable things this group -- that organization could do but I think it needs to be spelled out explicitly to sort of make that happen.

DR. SHAPIRO: Thank you.

Other comments?

Alex?

PROFESSOR CAPRON: Well, I wanted -- I just had a chance to read over again Alta's very helpful rewrite of 3.6. And other than some minor wording changes for (d) including the note -- noting that

there are now six, not five, conditions. I wanted to ask whether we have thought through what is listed under (c), which I gather is the replacement, intended as the replacement for the sentence in the draft for Marjorie that said an exception to this would be waiving consent in emergency research.

The language there suggests that such research can go forward under three situations, under three conditions, that it could not otherwise be done, no standard therapy exists, and all the research components offer the prospect of a direct medical benefit.

And I would wonder if people more familiar with this type of research from the medical side would think that those conditions are always going to be med in research. For example, if as part of a research protocol on some new drug to treat people who come in after a stroke unconscious to the hospital, which is the kind of situation one is dealing with, or after cardiac arrest. If the researchers intended to have a research intervention designed to monitor something which would not become part of the standard treatment if the intervention proved to be successful but is being done purely for research purposes, you are just trying to find out what is happening to blood gases or metabolites or spinal fluid or something during these interventions, and to see if that is a critical pathway that

differentiates patients who do well and those that do not, whatever.

It would seem to me that they -- that would say that that research could not be done. Now that may be the conclusion we want but I just want to be clear that that is what -- (a) what this says and (b) that we have recognized that that is what it says.

Is the point clear?

DR. SHAPIRO: I think the point is clear. Whether we really -- well, that is -- you are suggesting -- you are asking --

PROFESSOR CAPRON: I am asking -- I mean, there are people who remained -- who remain to this day very critical of the FDA's emergency research exception thinking that is too big an exception and that such research should be limited to situations in which you can get consent from somebody.

And this also, of course, does not have some of the other features of that which suggested a surrogate process of community involvement, other people who might be such patients going through a process. I mean, in other words, it is a very truncated thing.

But if we do go in this direction this would say that the research of the type that I just described that would have these additional purely research components would not be done or would be done without them in circumstances where perhaps the

researcher has good reason to believe that part of the value of the research is having those components that the research will yield less information and, therefore, not have as much scientific benefit without the information which such components could provide.

DR. SHAPIRO: Steve, then Bernie.

MR. HOLTZMAN: I think that is a very good observation. So we have three choices, right? The one choice is as written. No procedure if there is not a direct medical benefit. The second is such a procedure but if and only if it is minimal risk or less. And third is to -- even if it is more than minimal risk but that you re-aggregate your component analysis. So I am not comfortable with that as written. I am more comfortable with allowing the procedure with no direct benefit if it is minimal risk and I do not see how you can go past that without destroying your component analysis.

DR. SHAPIRO: Bernie?

DR. LO: Well, I think Alex raises, you know, one of these really tough perplexing cases. First, I think a lot depends on what -- how you categorize these components solely there to answer the research question. I mean, I think an extra LP is more than minimal risk. Arguably a CAT scan in someone that comes in that condition is not minimal -- is not more than minimal risk. So it would depend

on the details of the study.

You also, though, bring up a very important feature this leaves out, which is the community consultation/surrogate consent at a later moment in time.

And another way out of the dilemma Steve painted is to say that if the components that is designed solely to answer the research question involves more than minimal risk there should be a track they could follow so -- that might permit it and some of the things on that track might be some sort of community consultation consent from a surrogate or this national panel.

I mean, I would not want to totally foreclose research which might be extremely valuable but for good scientific reasons require these nonminimal procedures that are solely there for the research and not to benefit the patient.

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: I would like to apologize for having created confusion through sloppiness on my part when I was writing up this proposed recommendation for the e-mail circulation. It was not my intent to change the substantive requirements that are now in play under the emergency consent waiver policy that has been adopted or was adopted eventually.

I think that we might want to consider deleting sub (c) entirely as currently written and substituting some reference to endorsement of the current waiver policy in the context of emergency research and to not allow my poor drafting to get us off into an extended discussion.

DR. SHAPIRO: Other comments or questions?

Okay. Well, we have a lot of issues to consider and contemplate as we redraft this and redraft some of the recommendations along the lines that you have suggested here. So I want to thank you for all your thoughtful input on this and, indeed, for the thoughtful input over the last few weeks that I have been reading.

Let me suggest it is already five of 12:00 that we break now and remind you that public comment begins at 1:00 oclinicalock so it would be extremely helpful if as many of you as possible be back here at 1:00.

Thank you very much.

(Whereupon, at 11:55 a.m., a luncheon recess was taken.)

* * * * *

A F T E R N O O N S E S S I O N

DR. SHAPIRO: We have scheduled our public comments section of the meeting for this time at 1:00 oclinicalock. We are a few minutes late. I want to apologize to those who came expecting us to start at 1:00 oclinicalock for our public comments section.

We have two people who have signed up to speak to us. Let me just remind everyone what the rules are that we have adopted in this case. There is five minutes allocation for each speakers who wants to speak to us and, of course, if there are questions by members of the Commission following that, those are as, you know, perfectly appropriate.

The first person for public comment this afternoon is Vera Hassner Sharav from Citizens for Responsible Care in Research.

Ms. Sharav? Thank you. If you can press that little button, the microphone turns red.

PUBLIC COMMENT

VERA HASSNER SHARAV

MS. SHARAV: All right. I would like to say that my comments are based on the draft report as I saw it before today's discussion.

My name is Vera Hassner Sharav. I am going to speak on behalf of CIRCARE, Citizens for Responsible Care in Research.

I want to say that first of all we applaud the Commission for calling on Congress to enact

national legislation for the protection of human research subjects that would bring all human research, regardless of funding source, under one regulatory system of oversight.

We agree that a single agency outside of DHHS would be ideal, both to streamline regulatory requirements and to carry out the oversight task.

We also support the Commission for its recommendation in setting a strict absolute standard, if you will, for minimal risk but we are concerned about failure to define the upper limits of risk, pain and discomfort in research involving humans inasmuch as such standards are being established for laboratory animals.

We also applaud the Commission for its recommendation that will preclude the inclusion of cognitively incapacitated individuals in nontherapeutic above minimal risk research.

CIRCARE is also gratified that the Commission accepted one of our recommendations and that is for a no fault insurance policy for human subjects of research should they incur injuries.

The recommendations to upgrade ethics education for those involved in research are commendable.

However, there are serious concerns and omissions. First, it is no where stated in the draft that research is an optional endeavor and that human

beings have a right to refuse. All focus seems to be on how to get them to consent. Indeed, the recommendation to change the term "human research subject," a term that sets the proper tone for the endeavor, to "human participants research" wrongly conveys an equal status to research subject and research investigator.

The Commission makes no recommendation about enforcement and penalties for those who violate the regulations. Nor does it recommend the establishment of a federal databank to keep track of all human research subjects as is maintained for laboratory animals. Such a databank should also maintain protocols, consent forms and reports of serious adverse events. An annual report to the President and Congress would provide the much needed accountability that is currently lacking.

The Commission fails to adequately address the weakest structural flaw in the protection of human subjects. Namely the structure and allegiance of the IRB. As currently constituted, IRB members with the exception of one token outsider, are all employees of the same institution. Even the outside community member is selected by the institution. This is a built in conflict of interest that cannot be glossed over.

The gold rush frontier of medical science has, in fact, exacted an unacceptable human cost,

whose dimensions have not yet even been revealed. Secretary Donna Shalala called the current state of affairs "appalling and unacceptable," acknowledging that public confidence had been shaken by recent events.

Yet NBAC's draft report is strangely silent about recent public disclosures on the business of human experimentation such as the collusion of industry and academia and the pervasive conflicts of interest which now characterize the biomedical research enterprise.

Even expert FDA specialists have publicly raised concerns about undue influence by industry in the drug approval process. Serious adverse effects are glossed over, violations of informed consent are ignored, and harmful drugs are approved on the recommendation of FDA selected expert panels, the majority of whom have financial ties with industry.

Human subjects, which we estimate number 19 million a year, are put at increasingly greater risks of harm to speed up the process and increase the profits. That we believe is the unacknowledged purpose of the placebo control. The issue has pitted American researchers in the pharmaceutical industry against the ethical standards of the world medical community as articulated in the Declaration of Helsinki.

Serious adverse events, including deaths and

attempted suicides, are not reported even though they are required under current regulations. For example, according to NIH data there are seven million human subjects in federally funded clinical research, of whom one million are in intramural research at NIH. NIH's budget is $16 billion annually. Industry spends $26 billion annually for research, thereby increasing the number of human subjects by at least 12 million.

An analysis by Adil Shamoo of the data from OHRP from the last ten years that includes 70 million subjects in federally funded research shows that only 878 adverse events and only eight deaths were reported in ten years. Now the absurdity of that number becomes clear when we note that among the general population of 70 million the normal number of deaths is 600,000 a year. How could only eight deaths have occurred in a relatively sick population of 70 million?

Furthermore, prior to the disclosure of Jesse Gelsinger's death, less than 50 adverse events involving gene transfer research were reported during eight years. But following disclosure of his death the number increased 921 in four months.

We are especially concerned that there is an impending avalanche of enrollment of human research subjects before effective safeguards have been established. Animal protections have made it

increasingly difficult to use animals in laboratory research. As the New York Times reported, the use of animals as laboratory subjects had been declining in recent decades. Where do you think those who profit from animal and human research are turning when it is more difficult to get one species than another?

The fact is that the impact of animal protections has increasingly led those who need research subjects to use humans as experimental animals. For example, disabled patients, including veterans, are used in painful and highly speculative symptom provocation experiments that induce psychosis and safety experiments involving drugs that may adversely effect their developing brain receptors are conducted on children.

If left unprotected, this trend will be accelerated now that animal's distress levels are being minutely defined and regulatory prohibitions established.

20,000 children, some as young as three years old, are being recruited into drug trials that neither focus on life threatening conditions that these children may have nor even on well defined medical conditions but rather on the amorphous concept "at risk."

Pesticide toxicity is being tested on humans rather than animals and in some cases, such as the pollutant percolate, they are tested in humans after

they have bee linked to harm in people in the community.

Finally, I would like to correct the report's misrepresentation of the events which led to the Commission to make it's recommendations. Revelations about current unethical human experiments began in 1992 when the Aller family complained about a schizophrenia relapse experiment at UCLA that harmed patients. Criticism of that experiment in the press led to the birth both of NBAC and CIRCARE.

On September 18th, 1997, CIRCARE and ten research victims and families testified before NBAC about undue suffering caused by abrupt drug washout and chemical provocation experiments. We testified about widespread ethical violations, conflicts of interest and the absence of functional safeguards or accountability by anyone.

We informed NBAC that doctors and academia were getting up to $30,000 per schizophrenia patient they recruited into a clinical trial and stated that human experimentation on mentally disabled patients is out of control, there are no limits, no independent oversight, and no accountability for the human casualties of research.

Those testimonies set in motion a stream of investigations by OPRR, revealing major ethical violations in psychiatry, cardiology and pediatrics. As a result of those investigations, research at 12

major research institutions was shut down.

CIRCARE public's dissemination of information from our database reaches taxpayers, public officials, the media, as well a many NBAC Commissioners.

Our complaints about experiments that are designed deliberately to induce psychosis in patients for study purpose and to take PET scans led the director of NIMH to shut down 31 out of 89 clinical trials at the intramural NIMH facility.

Indeed, he found that 90 percent of NIMH's intramural clinical trials failed to meet either ethical or scientific standards, or both.

Thus it is surprising that the NBAC report fails to acknowledge both the events and CIRCARE's role in bringing pertinent information to public attention. Such information after all demonstrates the need for enacting a human subjects protection act.

DR. SHAPIRO: Thank you very much for your comments. Thank you very much for the material that you distributed. We have not only your testimony but we distributed the other material you brought to each Commissioner.

Are there any questions by any of the Commissioners? Questions?

Thank you very much.

The next person to speak to us Peter Lurie

from Public Citizen.

Mr. Wolfe is with him, I think. That is Mr. Wolfe -- Dr. Wolfe, excuse me.

PETER LURIE

DR. LURIE: I am Dr. Lurie, deputy director of Public Citizens Health Research Group.

This is Dr. Sydney Wolfe, who is the director.

Our comments are based on the draft handed -- the materials related to the public comments dated November 21st of the year 2000, which include a number of proposed revisions and our comments for the most part focus on those. That was at the meeting on the day before Thanksgiving.

Before I get to the one proposed change in particular, I want to briefly review some of our previous comments such that they actually get on to the record since the last meeting apparently did not count.

There are two issues, in particular, I raised last time that I spoke before this Commission, both of which represent positions to be taken under the current proposals by the NBAC lower than those of the Declaration of Helsinki, which is an international group.

The first was that the Declaration now states that medical research is only justified when there is a reasonable likelihood that the populations

in which the research is carried out stand to benefit from the results of the research. But the NBAC requirement on this has a -- sorry. Okay. -- is rather less clear and actually would permit research to be conducted even if the researchers did not expect the intervention to ever be made available in the community after the trial.

I think that is an enormous mistake and I think that really that needs to be revisited. It is true that you need to convince an IRB that, in fact, the study is responsive to the needs of the country but we think that that will be generally very easy to do given the conflicts of interest already well documented for American IRBs.

The second point we made had to do with what needed to be provided to the patients during a trial. Our first comment was that your proposal was merely for the provision of "effective established" treatment, unlike Helsinki, which requires the "best proven" effective established treatment.

We pointed out that that would allow second rate therapies to be provided to people as long as they were arguably better than nothing. Again you have to run this through an IRB but that leaves open a big loophole whereby if you can show that the only "relevant and effective study design" is that that would deny people even effective, let alone best effective therapy, you could proceed with your study.

Both of these need to be revisited because they are, indeed, lower than the now internationally accepted standards of the Declaration of Helsinki.

Now the document handed out at the November 22nd meeting makes the new proposal, which is that the American IRBs under certain circumstances could be cut out from the review of American research and that is also of enormous concern to us. I want to speak first from my own personal experience conducting research in developing countries, and I have done six or seven studies in such places. And in every case I was required to get American IRB approval, which I had never had any problem with.

In every single case the American IRB at the University of California, San Francisco as it happens, asked for some changes in my protocol and they were often very, very helpful. I mean in one case so substantial that we decided it was really more ethical to not conduct the study at all. So we got very useful comments from them in every case.

In every case when we sent it to a developing country IRB for review, all we got back was a one to two paragraph letter that never ever asked me to take any changes even though they saw the same protocol that the UCSF IRB saw. For example, I brought with me my approval here for a research project on needle exchange programs in Brazil and here is the review from UCSF, one-and-a-half pages.

They asked me to consider, and I agreed to, to conduct the study anonymously rather than with personal identifiers. They asked me to clarify issues related to reimbursement. They asked for a Portuguese language version of the informed consent form. And they asked me for five changes specifically in the informed consent form. All of which I made.

On the other hand, from the Brazilian side, I got this very brief letter, which you can see is no longer than a paragraph, and it says, "I have examined the research protocol with the following title. The research will be conducted by the following group. The proposed research is under the coordination of the following doctor. Needle exchange programs and their evaluation are very important to our state because of its high HIV prevalence among injection drug users. The school of medicine supports the proposed research and looks forward to collaborating actively in its investigation."

No suggestions to me. No requirement as the UCSF did for continuing review, sending things back on an annual basis. Just really quite -- very rudimentary. That is what I got every time when I did this kind of work.

We do not take the position that American IRBs are so great that they are inherently better

than foreign IRBs. Certainly the Department of Health and Human Services has documented on two occasions at least quite -- the problems with American IRBs. But the data collected for the NBAC make a very compelling case that at least at certain times (a) the developing country IRBs are inadequate without making any statement about the quality of American ones; and (b) that the American IRBs very often add another layer of very important protection for subjects.

We do not really understand -- well, let me let that go. Let me give an example of the kinds of things that were raised in research conducted for the NBAC.

Developing country researchers made the following comments: "The Ministry of Health is more concerned about the money than whether the study is okay for the people or not."

"The local IRBs are not really concerned about ethical issues. They are looking at technical issues and you know who is giving you the money, how much you are getting, but now we need to look at the ethical aspects. What people are doing. Is it right?"

"They, the pharmaceutical companies, get an institution somewhere that has a person that could be willing to just take them in and do whatever kinds of studies they want to do."

"But in terms of who is running these bodies and who is controlling what is really happening, you will be amazed. It is mostly people who have no idea about this. They just know it, ethics, is a word."

"The biggest problem in developing countries is that our poverty puts us in a situation where the beggar has no choice."

These are direct quotes from volume 2 of the data collected for you by the Johns Hopkins University. Not one of these quotes appears in volume 1. We are very troubled by that.

Quotes from industrialized country researchers, also collected for you, are similarly not found at all in volume 1. Perhaps because they are inconvenient. This one from an American researcher: "Some of the developing IRBs do really quite a decent job just as you would want them to be and there are others that are completely rubber stamps and nothing else. Yes, there is an IRB but I do not have any faith that there was any real review."

"In some cases the developing country ethical review is actually a process of seeking permission to conduct research and no ethical questions are raised at all."

That is precisely my experience seven times out of seven.

"Developing country review boards are often

more concerned about the financial aspects of the study than about the ethics."

Again, none of this appears in volume 1 of the report, which is likely to be the only part of the report that is widely read.

Finally, there are data that have been collected by the Johns Hopkins researchers that are absolutely relevant to this -- the matter of whether or not there should be two IRB approval and many of these are not in volume 1 at all and some -- and others are just really not afforded any great attention.

For example, it turns out that actually many people are --

DR. SHAPIRO: I am sorry to interrupt you but you are well, well over your five minutes. Are you about to draw your comments to a close?

DR. LURIE: I am absolutely drawing to a close.

DR. SHAPIRO: Thank you.

DR. LURIE: It is -- firstly, many places are, in fact, getting what we might call double IRB approval. 91 percent of university studies, 100 percent of U.S. Government studies, compared to only 22 percent of the pharmaceutical industry. What you might have done was extended the requirement to the pharmaceutical industry rather. Instead you are actually lowering it and taking a requirement away

from people who, in fact, are getting two IRB approval.

The second point I would like to make is that among U.S. respondents, they identified a number of things that the U.S. IRB was more likely to bring up than the developing country IRB even though you might consider these things to be typically developing country concerns.

The U.S. IRB was statistically more likely, according to these American researchers, to ask whether the intervention was too risky, what were the research procedures for the control group, use of placebos, whether the benefits might -- offered might compromise voluntariness, the relevance of the research to developing country, post-trial availability, complexity of informed consent form, need for local language.

Every one of these things was statistically significantly more likely to be requested by an American IRB and none of this information appears in your report.

Finally, the CIOMS and Canada require two IRB approval. And to my knowledge, at least, this would be the first ethics document that would specifically allow only the developing country to conduct such review.

Thank you.

DR. SHAPIRO: Thank you very much.

Thank you very much, both of you, for coming here today.

Before you leave, are there any questions people wanted to ask or comments from Commissioners?

PROFESSOR CAPRON: Peter, what is your view about review in the United States of a protocol in which an American researcher joins with colleagues at a second institution to do research and the research is approved at the institution where it is going to be done? Should it be also reviewed? Should it also be reviewed at the institution from which the individual comes?

DR. LURIE: I presume your question means a second American institution?

PROFESSOR CAPRON: Yes, two American institutions.

DR. LURIE: Yes.

PROFESSOR CAPRON: Domestic research.

DR. LURIE: Yes. Our feeling is that there needs to be review at all of the local institutions in which the research will take place, whether those secondary institutions, if you will, are in the United States or abroad.

PROFESSOR CAPRON: Thank you.

DR. SHAPIRO: Thank you.

Any other questions?

Steve?

MR. HOLTZMAN: Thank you for your comments.

I think -- I am not sure I understood the answer to that but I have the same question. I do not think -- well, let me ask this question: Are you saying, in principle, two IRB reviews are always better than one and, wherever possible, one should have more than one IRB review or will one good one do?

DR. LURIE: Well, the answer is that more than one institution is involved. Wherever the second, third and fourth institution is, there should be a review by the second, third or fourth institution because my experience, and I think in the experience of others, and in the experience documented in the data collected for the NBAC, in fact, the second IRB in the case of their data, the American one added important additional information.

But I think our allowing -- as long as an American funding agency, in particular, is involved, to remove American review from that process, I think, is really quite dangerous.

MR. HOLTZMAN: Why I am asking the question the way I am, Peter, is, for example, let's just stay within the U.S. and it ties to Alex's, we are dealing with the issue of multisite trials and whether or not there is a more equally effective but more efficient way of dealing with it such as a central review by one IRB.

Now if one is saying, no, in principle, if there is more than one institution, they all have to

be involved, then one should presumably be saying that because there is an improvement in quality.

With respect to the international situation, we did not flat out say we will defer to the international or the other country's review, the intent of it was, was if that country had come to a standard of human subjects protections equal to ours. So that is what I am trying to get at. If that intent were fulfilled, whether in principle, you would still say you still have got to have more than one or whether your concern is a factual one about one will do if it is, in fact, of the standard but it ain't there yet. I am trying to get at the basis of your objection.

DR. LURIE: Well, one part of my objection is that the proposal 5.6 does not actually say what you describe. It does not require any finding of "equivalence" before the American IRB might absent itself from the process and it does not require that. In fact, it just simply says --

MR. HOLTZMAN: 5.3. 5.3 talks about identifying country -- the intent of it, is my understanding, that we would identify countries with an equal standard. Now 5.6, maybe we are working with different numbers and it is different.

DR. LURIE: No, 5.6 does not say anything having to do with equivalence. It simply says that, you know, there must be approval by independent

ethics review committee in the country where the research will take place, period.

Whereas, it used to say where the research will take place, as well as by U.S. IRB.

DR. SHAPIRO: We can -- I think we can help clarify this issue.

MR. HOLTZMAN: That is not what it says.

DR. SHAPIRO: I know.

Eric?

DR. MESLIN: Peter is referring to materials that were handed out on the 22nd for the teleconference. There was no description in those materials that Peter is referring to. However, during the course of both that conversation and then follow-up e-mail the Commissioners continued to discuss this issue and I think Peter is aware, both from discussions our office has had with his, that the Commission continues to discuss that specific issue of making very clear that the number of IRBs required is linked to the issue of equivalent protection that was discussed at the meeting that you know was not an official meeting. In fact, a number of Commissioners expressed their own worry with the lack of clarity in the staff proposed material.

I do -- I do not want to make it a debate about which numbers and what saying but I will say that the materials that the Commission is going to be discussing tomorrow make that issue very, very clear

and make a number of suggestions for the Commissioners to consider that links the number of IRB reviews required to the issue of equivalent protection.

I am happy to share them with you. We hope you are here to hear the discussion so that you do not misjudge what the status of the discussion was at any one point in time.

DR. LURIE: Well, of course, you know, I am basing my comments merely on the documents that are available to me so that is why I say this.

We have concerns about the notion of equivalence, however, and in particular the notion of equivalence has meaning only when there are very, very concrete criteria that would establish such equivalence. We are aware, too, that American law currently provides for equivalence but we know, too, that as far -- to our knowledge, only the USAID has ever actually developed such criteria and they have never implemented them, and other people have shied away from it, I would imagine in part, because they have imagined it would be very, very difficult to do.

There is enormous variation within countries of IRB approval much as there is within this country. And so how one would even set about establishing equivalence either on a national level, institutional level or hospital level, I frankly do not know.

So,to us, particularly because historically

the American IRBs have provided a unique contribution according to the data collected for you. We think to remove them from the review of certain American funded research would be a mistake even if particularly in the absence of anything showing equivalence.

DR. SHAPIRO: Thank you very much.

Any other comments or questions by Commissioners?

All right. Thank you, both, very much. We very much appreciate you coming today and we certainly thank you for your thoughtful comments both last time and this time. Thank you very much.

Although, we are out of time, I would like to ask if there is anyone in the audience who would like to address the Commission very briefly.

Thank you very much.

Let's then return to our agenda.

I would like to make a proposal, if the Commissioners would agree, that rather than going to chapter 4, Marjorie has indicated that it would be most helpful to her as she begins to redraft all of these items we are bringing up, to turn to chapter 2 first. Is there any objection to proceeding to chapter 2 at this time?

Okay, Marjorie, let me turn the discussion over to you and we will focus on chapter 2.

DISCUSSION: CHAPTER 2, "A PROPOSAL FOR

OVERSIGHT"

DR. SPEERS: Okay. We, in part, thought we would focus on chapter 2 because where our discussion was going before we broke for lunch was to -- I think where you were headed was to talk perhaps about the definition of human participants research and particularly something about identifiable data, the use of identifiable data.

So to continue where we were before we broke for lunch, I thought we should move to chapter 2, and then I think we have enough time in the agenda that we will go from chapter 2 to chapter 4, and then the recommendation in chapter 5.

DR. SHAPIRO: Where do you want to go?

DR. SPEERS: So, I guess, where I would like to start is let's -- based on what I have just said, let's start then with recommendation 2.3.

DR. SHAPIRO: Okay. 2.3. Are there any comments, questions, observations from members of the Commission with respect to 2.3?

Alex?

PROFESSOR CAPRON: Just to begin with a very minor one, in the first bullet I gather that the purpose of this statement is cautionary. That is to say is to recognize that the interests of the subject by definition in research -- I still cannot use the word "participant." I mean, I am with those who think that we lose more than we gain by that blander

term but I will say "participant." That to say that it is secondary is to say -- is to make a statement of the reminder of this.

It is not something where you could say, well, I am not doing research because, in fact, I want to help subjects even more than I want to contribute to science. Is that correct? It is sort of -- it is an imposed definition. Or am I wrong?

DR. SPEERS: Well, I think to speak for the Commissioners and some of the previous discussions on this issue, I think it was the sentiment to work into a definition of research, to be very explicit in that definition about the nature of the relationship between the investigator and the participant.

We have -- Commissioners have used terms that participants are essentially a means for the investigator and so I --

PROFESSOR CAPRON: Well, Marjorie, my point is not the substance of that. It is what role it plays in this statement. It is one thing to say that I know something is research because it is designed to produce generalizable knowledge as opposed to provide a benefit to an individual or something. I mean, it is another thing to say that I know something is research because the interest of the participants are secondary to those of the research.

In the latter case it seems to me something which I might describe as research would be described

honestly if maybe I would think misleadingly by someone else engaged in it by saying, oh, no, my intent is to benefit these people more and, yes, I will get some generalizable knowledge but I always have their welfare in my mind.

Now to me that would not change it from being research if it met other criteria. So this is the difference between a general description of the fact that it is usually the case that in research the interests of subjects are secondary and one of the problems is that people often forget that and particularly the subjects forget that -- excuse me, the participants forget that. But you see the difference so I do not understand the role of this bullet here.

The other bullets seem to be a way of an IRB deciding is what is being presented to them appropriate for their review because it is research or should it just be off the table because it is not research. This seems more a comment on the general activity. Am I making myself clear?

DR. SHAPIRO: Larry?

DR. MIIKE: Yes, I agree with you, Alex.

I think if we want to keep this thought in it really should be as part of the bullet in the bottom that describes what human participants are. It says the research involves human participants. And we can say something in which the relationship is

unequal and that participants are used by investigators for the objective of the study.

If the thought -- I agree with you that it really is not part of the definition -- this is a two part thing. It is a definition of research and a definition of human participants.

PROFESSOR CAPRON: I do not even think it is -- you see, Larry, I do not even think it is a definition of the human participant because I can again imagine situations -- you are doing research and the participants in the research are the chairs of the departments of internal medicine at the leading university, they know as much, they are higher status, they have more power than the researcher.

DR. MIIKE: No, I am not referring to --

PROFESSOR CAPRON: And so --

DR. MIIKE: I am not referring to the first bullet, Alex.

PROFESSOR CAPRON: No, I know, but even if you --

DR. MIIKE: The intent of this recommendation, this part of the recommendation is to say what is research and what is human participants. All I am saying is that if we want to keep this thought that this in the first bullet in the recommendation then we use it as a description leading into the definition part of human

participants.

PROFESSOR CAPRON: And I am saying even as to human participant the kinds of things you begin to draw out that they are in a lesser position or dependent or something vis-a-vis the researcher, I can imagine research done with people who do not fit that and yet they would still be participants.

To me, for once, this is something I think you should be urging us to be put in the commentary. It is a generally true statement and it is one of the reasons why we go through all these activities of review.

DR. MIIKE: Agreed. Agreed. But I am saying that if we want to keep the thought in, okay, that is all I am saying.

DR. SHAPIRO: Other comments?

Bernie?

DR. LO: I will agree with sort of moving that bullet into the text.

As I read the text that goes through recommendation 2.5 -- sorry, 2.3, 2.3 was clearly motivated by activities which under the current definition are just very difficult to categorize and, in fact, tend to get characterized as research, although the text suggests they really should not be characterized as such.

I am wondering if we should sort of be a little more forthright and if we really believe that

things like -- I mean, the examples I underlined, Marjorie, on 28, journalism, marketing surveys, political polls, routine public health practice, evaluation of programs on page 30. That we do not think is research and we really want the NORE people to sort of define it as not research. I think we should say that and if we think our definition, in essence, does that for us, we should have a little side bar showing how all that stuff really does not count as research under our definition.

Otherwise, I think it is not really clear to a reader how our definition is superior to the current one and it clearly has the problem of taking up more words. So I think it is better but we need to explain why it is and go back to our problematic cases.

DR. SHAPIRO: Bette?

MS. KRAMER: I would like to go back to the problem I raised earlier. Well, I raised the example in the twin studies. Looking at the text on page 33, line 28, we make the statement generally these other individuals are not considered participants in the research, talking about family histories, et cetera. And yet when you go over to the recommendation itself, the bullet at the top of page 37 seems to capture these people in the definition of human participants. So to me there is a lack of clarity there and I can see where it is going to continue to

be a problem for the people who are trying to do this kind of research and dealing with the issues around informed consent.

DR. SHAPIRO: Other comments or questions regarding 2.3?

Steve, and then Jim.

MR. HOLTZMAN: I want to try to do this in a way that does not refight the battle I lost with biological materials but if you go to the last bullet "identifiable data about them are analyzed" we have just raised the prospect of records research and tissue research where it is identified in the repository and provided in a coded manner to the investigator.

If you go to page 34 of the text where we talk about identifiable, it is a very striking feature of that text that we discover that as opposed to what was told to us at the time of the HBM report by OPRR that coded always is identifiable. There are, in fact, cases where it is not considered identifiable and these are referenced on this page.

And I would like to first off just point that out.

Second off, if you look at the work of -- and I would love for Bernie to chime in here -- the work of the IOM and others, there is an approach which says it might make a lot more sense to look at records research, tissue research I think of as a

subset of records research, and focus on the protection of the privacy of the confidentiality with appropriately constituted boards that do not necessarily at all look like IRBs.

So do not define them as human subjects research the way we are doing here and then try to twist them into the regulations but say if you are conducting research where there is no implication for the -- there is no individual identifiability, as long as -- what you should be focusing on is the protection of that confidentiality through data safety review -- not data safety. What is the word? Bernie knows the right terms that are used in this sphere -- confidentiality review boards or whatever with experts who are experts in things like coding systems, computer systems, internet systems and whatnot.

And I think it is an approach that is not my idea. It is all around us and many groups are working on this and I am just wondering -- I think we at least -- if we are not going to go down that path we ought to at least talk about why we are not.

DR. SHAPIRO: Thank you.

Jim?

DR. CHILDRESS: A couple of preliminary points if I could while I am thinking about this subject area. One would be in terms of Alex's comment about subjects and participants and I have no

objection to our going to participants but I do not think we ought to devalue the term "subjects" and forget actually how important it was in the early discussion of research involving human subjects to be able to distinguish the subject from an object and the means and so on and so forth.

I mean, after all, Eric Cassell is not here but his work on subjectivity -- I mean, we are talking about something that the subject is not -- I want to say sort of diminished in value when we use that language, though again I have no objection to going with participant.

However, in terms of the title I do have an objection just to having human research. And I cannot remember, I may not have been in the meeting when we ended up going in that direction as the title. I would prefer that we say at least in the title "oversight of research involving human participants" and then if in the text we want to use a short-hand expression "human research," I would have no objection to that but I do think in the title that we can indicate what we are about a lot better if we use the more cumbersome expression.

Now along the lines of the discussion we have just had let me push in a different direction, Steve, but indicating I probably would end -- I think I would end up agreeing at some point with a recommendation along his lines.

But I just want to be clear about something. We -- I am not sure that our discussions in the text here pick up all that is important from our human biological materials report but let me just raise one question. Excluded from the definition are deceased individuals.

Now I am not convinced that what we have done in human biological materials report will actually always exclude deceased individuals because consider, for instance, we say that research conducted with coded or identified samples is research on human subjects and regulated by the Common Rule. Now that is in our report of human biological materials and you can have coded samples of deceased individuals. They can be identified. It can have an impact on their -- the way they are viewed by those who survive, et cetera, et cetera.

So I am not -- I am not convinced that we in our previous report really totally excluded them and we probably ought to make the case strongly here and indicate our argument here is different. I may be wrong about my reading of the -- of our previous report but at least I think the case can be made in terms of the language we use that that is what is involved.

I will stop there but again in saying that I was really calling for a kind of clarification relative to where we were in the other report and the

kinds of arguments we might be offering now but saying that probably I would end up going -- I could go in Steve's direction.

DR. SHAPIRO: Bernie, did you have anything?

DR. LO: Yes. I wanted to think through the implications of our definition because as we have said all along, different provisions interlock and lead us in different directions.

Traditionally the definition of who is the subject of research has two implications. One, does the IRB have to look at it? And, secondly, there are implications about consent.

One thing that we do not address is this who gets to determine if it is research or not? Does the investigator on his own or her own make that determination? Is there any overview by a more disinterested party because there is actually some incentive for an investigator to say what I am doing is not research and, therefore, I do not even have to show it to the IRB.

So there are issues of whether -- even if it is not research do you have to have someone check that you have made that determination in an appropriate manner?

My second thought is that in the current regulations asking whether or not something is research has tremendous implications in some situations for whether you have to get consent from

the subjects. And I guess I would sort of -- trying to follow the line of thought that Steve was laying out, I think consent is one of those things that has been very important and, however, tends to be over valued, and I think one of the things that has happened is we spend so much time focusing on do you have to get consent from the individuals who are you studying in some sense that we lose sight of balancing of risks and benefits.

I would argue that for research on existing data collected for other purposes or stored tissue samples, the crucial ethical issue is not really consent of the individual. It is whether the balance of benefits and risks is appropriate. It seems to me the IRB really needs to make its determination. I think we have kind of addressed this in the HBM report.

First, is the research question significant enough that, you know, there is some benefit. And, secondly, let's really look at the risks and I think I would agree with Steve's view that for research on existing records and materials, the real risks is that of breaches of confidentiality.

I would submit, and our IOM panel went into this in some length, that IRBs as currently constituted really do not pay enough attention to the matter of the risk of a breach of confidentiality. In particular, do not really have a robust tool box

of thing that investigators can do to really lower the likelihood that either an inadvertent or an intentional breach of confidentiality will occur and there are just lots of things ranging from technical advice on how to store the data, how to code the data, how to transmit it from one researcher to another if it is a multisite study, to the organizational framework of confidentiality -- policies that would make a huge difference in sort of what level of risk of breaches of confidentiality we are talking about.

It seems to me that one way to look at this type of research is to say that if appropriate steps have been taken to really protect confidentiality and the breach of confidentiality is the major risk, once the IRB or the more -- or some body has determined that and also determined that whatever a risk is, it is worth a potential benefit arising from the study, then we may presume that it is okay to do the study without trying to get informed consent from the subjects.

It is a very different way of looking at it than focusing on do I have to go out and sort of send postcards to 10,000 people trying to get them to participate.

DR. SHAPIRO: Okay.

Larry?

DR. MIIKE: Well, two things. One is that,

Jim, I do not believe that in our HBM report that we made an exception for dead individuals as still being human subjects. And then also in that report we did talk about practicality issues around -- about getting informed consent. So those kinds of issues have been addressed and we can still be consistent.

But, I guess, the main thing going on over here is that we had a discussion a long time ago about are we going to try to have -- try to be very inclusive in our definition and then being so are we going to then try to draw up a whole list of exclusionary categories. I think we decided that that is not something that we could do so we opted for very large inclusion and then leave it for experience and just the application side to decide on these kinds of issues.

So to me here it is not so much our discussing which things should maybe not be included in the human subjects research, et cetera, but just to have language in there that gives flexibility to the system to deal with these kinds of practical issues because we are -- we have deliberately chosen a path that potentially is just overwhelming in terms of the number of projects that would be coming under the purview of IRBs and we have got to make that responsibility more practical in terms of the application.

DR. SHAPIRO: Steve has his hand up but let

me just ask, I think, a clarifying question here. As I understand 2.3, it is attempting to accomplish a number of things. One is to define research. Okay. And that is under a couple of these bullets. I think it is the second, third and fourth bullet, the one on page 38.

The first bullet is not anything to do with defining research. The first bullet has something to do with inaugurating protections of some type. Right, you might want to offer protections because there are these conflicts. I mean, that is what the first bullet deals with.

And I think Larry is right. If we want to keep that at all in here, it really belongs over in the human participant -- on the human participant side. But the main issue I wanted to raise, Marjorie, is whether we really want to define research and those research projects for which special protective measures are necessary really in the same -- at the same moment. Is that really trying to get too much out of this definition?

We are trying to define research and we are trying to define human participants and we are trying to define who needs protection. All that is rolled up in here as I understand it.

So I am asking a question and not -- I am trying to ask a question I mean.

DR. SPEERS: Right. Okay. I think I

understand most of it. What we are trying to do here is to offer guidance so that our regulatory definition of human participants research could be developed. We are in this recommendation suggesting that the definition be a definition that defines human participant and defines research at the same time. That is based on the way things are done in the current system, which is first research is defined and then a human subject is defined, so it becomes a two step process, and we are trying to combine it here into one. If you want them to be separate we can separate them.

I am lost. I do not think -- I do not think that we are trying to necessarily talk about the protections here so I am missing that if that is what you -- if you think we are doing that.

DR. SHAPIRO: I did not mean to say we were talking about protections. I think we are trying to define a population for which protections might be appropriate.

DR. SPEERS: Right. And I think -- I think a we have discussed before, a definition can only go so far in defining what it is that we want to regulate under the oversight system. It is going to take leadership from an oversight office to provide that additional clarification of exactly what is in and what is out and new examples are going to come up all the time.

So I am not sure we can do it a whole lot better than we have tried to do in this recommendation other than what we have said because I think the specific example would have to be worked out at a later date.

DR. SHAPIRO: Alex, and then Bernie, and Jim?

PROFESSOR CAPRON: I do not think that the definition has the problem that the chair has just suggested but I do think it has problems and I thought that what Bernie suggested earlier about our asking in what ways does this definition improve upon the existing one is something that is a very important task because we are, in effect, saying rewrite the definition and the way we are going about it is better.

The third bullet, which says the results have validity, and then it explains what that means in that what is learned about the particular scientific problem can be justifiably claimed to be true for all like scientific problems or facts, I gather, is a way of covering the same ground but in what you regard as a better way than the word "generalizable." Is that correct?

DR. SPEERS: Yes.

PROFESSOR CAPRON: I have a problem with the expression of this particularly when you go on to explain parenthetically that a marker validity is

publication or presentation of the results. Clearly as the IRB looks at something, the most that can be said is that if the research is carried out in the way in which it is described and if it has the kind of results that the investigator expects, it might qualify to be regarded by people in the field as valid in the way that you are describing it. That is to say suitable for publication.

But there is a lot of research, which although carried out according to plan, comes up with results which are regarded as too equivocal or just not proving anything on way or the other, not because the research was carried out wrong but just because it fell into that category where the results are not statistically significant or whatever.

Now anything that speaks in the past tense or -- maybe it is not the past tense but the present tense as to results, which is a -- is -- it just is not going to work there. I mean, at the most you can say that it is designed so as to produce results which have the ability to be justifiably claimed to be true for all like scientific problems and I am not sure that that is a huge advance over the way the word "generalizable" is usually understood, frankly.

Is -- because otherwise I see you saying that an activity is research if it intends to produce new knowledge which includes not just facts but also principles or theories or information and it can be

new in the sense of a whole new area or something which simply refines or improves on existing.

Secondly, that they have to be true not just for the individual subject, the individual person on whom they are gathered but in the manner in which this process is carried out they will have some wider generalizability that the process is systematic and that a human being is involved as a participant. That is how we know that it is research. That is what we are trying to say, right? And the claim is that that does as better job of doing it than the present definition.

DR. SPEERS: This is not a definition of research. What we are giving here are the characteristics that we would want to go into a definition that should be developed.

PROFESSOR CAPRON: Well, I understand that answer to mean we are not yet prepared to write the language of the regulation but the regulation is a regulation of a definition. The sentence begins with such a definition should include the following key features.

Now if we were really bold we would write the definition but given the difficulty that this group has of --

MR. HOLTZMAN: Of being bold.

PROFESSOR CAPRON: Excuse me.

MR. HOLTZMAN: Of being bold.

PROFESSOR CAPRON: Not of being bold but of the time constraints that it would take collectively to do this and I think the sense that that process quite legitimately gets input from more actors than we have around the table at the moment.

What we are saying is it ought to look like this, the exact language remains to be defined. So I think it is a dodge to say that it does not cover this ground.

But if we say one of the characteristics is that the results have validity we have said something which is not true at the time that you begin and I do not know how you would write a definition that does that if you see what I am saying.

DR. SHAPIRO: Okay. I have quite a few people who want to speak. I think it is -- the point you make of past tense I think is quite correct in this case. It has to be drafted in that way and there are other substantive issues here.

There are a lot of people who want to speak. Bernie, you are next.

DR. LO: Well, I am wondering if instead of focusing so much on sort of what ought to go into a new definition of research. We clarify why we -- we say why we think clarification of the definition of research in human subjects is important. It seems to me there are three reasons it is important.

One is that there is misclassification.

Some stuff does not get considered research that an IRB ought to look at and, therefore, slips through and we think it is problematic.

On the other hand, the reverse also happens. Some stuff gets dragged before an IRB which does not need to go there and should not go there and clogs up the IRB, and does not really protect people.

The second reason for trying to seek clarification is that it is not the definition of is it research or not, it is sort of the downstream implications of what you have to do with regard to consent from individual subjects in research that is really growing by leaps and bounds. The -- you know, the research on existing data and materials. And I think that, you know, since we are saying anyway come up with an improved definition of research, rather than telling them how to do it, maybe we should say do it so it accomplishes the following goals or at least helps resolve the following problems.

DR. SHAPIRO: Jim?

DR. CHILDRESS: If we look at part of the -- I very much agree with the direction that Bernie has just gone. If we -- there is an ambiguity in the term "covered activities" and covered may simply mean covered by the definition but the way in which this flows it looks like it means covered by the kinds of protective mechanisms that we think are important. This is in line four. And I think it is especially

true because of the way in which we have covered -- limits covered activities to those with associated risk of harm.

I do not think there is any way we could justify to come up with a definition of research and human participation that is limited to those that involve risk of harm. I mean that is to miss the kinds of differences that we would be concerned about on ethical grounds, for instance, between wronging someone by using someone even though there is no harm involved, and obviously those are the kinds of things we will work out when we get to minimal risk and the like.

But I do not think we can deal with that under a definition and I think the definition has to be focused in other ways and then we come up with the kinds of exceptions regarding coverage according to things that have to do with the degree of risk, for example, and whether the risk is primarily from the breach of confidentiality and privacy but I do not think that is the -- what we can accomplish in a definition.

DR. SHAPIRO: Arturo?

DR. BRITO: Is this --

DR. SHAPIRO: If you just want to reply to what Jim just said.

PROFESSOR CAPRON: It is just to Jim. Jim, I think you disagreed with Bernie and I agree with

your conclusion, which is we should -- as I understand it, we should separate our attempt to define research from a separate question. If it is research what procedures should be followed for that category of research.

DR. LO: I would agree with that.

PROFESSOR CAPRON: Oh, you would. Okay. Then we are in agreement. Good. I was afraid that you were saying that it has to serve both those purposes.

DR. LO: No.

DR. SHAPIRO: Arturo?

DR. BRITO: I will keep it brief because I am finding myself in agreement with a lot of the points that Alex raised on this third point here under 2.3. So especially with the text, I think it is really an important point because I think when we define research, in reading this it -- that was lost in the there somewhere. The research is being defined as the participants are being enrolled or recruited, et cetera. So I think it is a very important point he raised on that.

The only thing is I think some -- at some level the point about generalizability that is discussed in the text, that really needs to be taken care of one way or another where if there is clarification or if there are suggestions for clarification because that is a sticking point in

many IRBs and how do you interpret that, and there needs to be some guidance in there.

DR. SHAPIRO: Thank you.

Steve?

MR. HOLTZMAN: Well, there is never a right answer between lumpers and splitters, right.

DR. SHAPIRO: Right.

MR. HOLTZMAN: You have to make -- whichever way you go you have got to compensate for it, right?

So to try to avoid that I find it very useful -- well, first a few points. First off, I think that what Marjorie was trying to do here was not give the definition but say that you, NORE, when you draft your definition, here are things you need to address and give examples and guidance, et cetera, because it has been unclear. And I think the way we have drafted it here, Marjorie, I do not think it works that well but I think we can make it get there, first off.

Second, I do not think there is any way of saying -- if you are talking about human subject or human participant research, the idea that you are defining those two together versus -- it is two parts. It is what is research and what is --research on what? Humans versus animals versus whatever. You cannot get around the fact that you are going to end up defining both of those, right.

So for me at that point I find a big

difference between interventional research where I actually have contact with the subject versus records -- let me call it records research, noninterventional research. And if you look at our -- when we come to what is a human participant, you have the exposure to manipulations, they provide data. There is the actual interaction between the subject and the individual so that there is opportunities for consent. There is issues of autonomy and everything else.

For my money I would then either say human subject research includes two kinds of research, interventional, noninterventional, and it so happens I would want to think about them very differently. All right. Or I would say human subjects research is a paradigmatic where you have the interaction with the person and then there is this other stuff, call it records research, all right, and records research only starts to involve some of the apparatus of human subjects research if there is a potential for a breakdown in confidentiality.

So my recommendation was not -- and I do not want to be misconstrued -- was not about trying to get records research out from under a regulatory scheme. Quite the contrary, I think we have got too weak a regulatory scheme for what is going to be a very broadening area of research that can harm people but where the harms are not about batteries or

autonomy rights so much as they are about breaks in confidentiality, and I would like to see a regulatory scheme that is able to address that appropriately. I do not think that IRBs are the way to do that. I think there is a different kind of board that is the appropriate way to do that.

DR. SHAPIRO: Thank you. Marjorie, do you want to comment?

DR. SPEERS: Yes. I wanted to comment on that because that is a similar point, I think, to what Bernie made earlier and so I want to ask the following question: I think under the system that is being proposed here that this system allows the flexibility that it would -- that we seek for reviewing different types of studies.

So that, for example, it would allow an institution or it would allow guidance to be developed that for studies, record review studies, that those could be -- those could be eligible for an administrative IRB review, and there is nothing that would prevent an institution for setting up an entity -- you know, one person, two person, three person group that only reviews those types of studies.

That could be done.

So then the question is -- so my question then to you is, one, do you see that flexibility in this system and, if you do not, then is it something that we need to emphasize because I see it running

throughout, whether it is in the type of review that is done, the analysis of the risk and potential benefit or the requirements regarding informed consent or waiver of informed consent. I see the flexibility there. It has to be further developed through guidance but I do not see anything that prohibits what you and Bernie have suggested.

DR. SHAPIRO: Steve, and then Bernie.

MR. HOLTZMAN: I think it is the case that nothing prohibits it so I am advocating something stronger than just merely being allowed or prohibited, and I am also suggesting that the conceptual framework in which it is built does not lead you there and it twists -- you get all twisted in your socks or whatever trying to get there because you start with the paradigm of a human subject in a doc's office getting an experimental therapy, and then you twist and turn away from it trying to get to what you are really caring about.

I do not think it works and I think it ends up misleading and what we have been bothered about for years is we keep saying that these things do not give clear direction in our very report, right. We say an analysis of identifiable samples is human subjects research -- oh, but by the way on page 34 it is not always -- I think this is our opportunity to address that kind of problem.

DR. SHAPIRO: Okay. I have two people who

want to comment. Bernie and then Bill.

DR. LO: Yes. Marjorie, I think you raise a very good question and I would say that there is nothing that prohibits it but we want to sort of encourage that kind of flexibility and to make that something that IRBs seek after and we need to sort of figure out what this flexibility means here. We do not want it so flexible that things get out of hand.

What I think you are also asking is a question we do not really address in this report and I think we should, and that is sort of why do we have IRBs and do we still believe that IRBs are basically a good thing as one of the, you know, twin pillars we used to talk about. Because it seems to me that a way to frame this discussion about certain types of research is that IRBs need to have the expertise to deal with the kinds of problems, ethical problems and technical problems that come up before it, and just as we said in the Capacity Report that IRBs that spend a lot of time dealing with subjects with questionable or impaired decision making capacity ought to make very sure that composition gives them that kind of expertise, including people, you know, knowledgeable from a patient point of view.

I think once we start to say let's differentiate, let's have the IRBs differentiate or specialize, or adapt to the kinds of research they are seeing, which may be different than their

traditional paradigm, then the question comes up as to whether composition of IRBs that deal with DNA testing on stored tissue samples or that deal with health services research on huge databases collected for other purposes ought to have a different composition than an IRB that deals with clinical trials or translational research or social science research for that matter.

And I would argue that again the IOM report suggested that expertise in data management, computers, statistics, internet things, that is the kind of data -- that is the kind of expertise that IRBs typically do not have but really go to the heart of evaluating the risk posed by a health services research protocol.

And, similarly, I think if an IRB is seeing a lot of research, genetic research on stored tissue samples, the Mayo Clinic model that Chris talked about where, you know, an IRB that really specializes in that, helps genetic expertise as well expertise about how you file these samples and how you access them and code them, that would really go a long way to reassuring people whose samples are being used that their confidentiality is adequately protected.

So I think to answer the question you posed about encouraging flexibility, you also have to address the question of what are we thinking IRBs can do and how do they need to be revitalized or changed

or reengineered, whatever the verb is, in light of all the criticisms we have seen of IRBs in the last couple of years because it is kind of interesting that given all the criticism of IRBs we do not really address do we still think they are a viable means of assuring human subjects protection.

DR. SHAPIRO: Larry. I am sorry, Bill. You are next. Sorry.

MR. OLDAKER: I do not know that I really have a lot to add other than I agree with what Bernie and Steve have said but I think that in my mind that, you know, there are two important considerations as far as regulations. One is on the -- when you are -- some sort of intervention is going on. I think we want to have one type of IRB always out there.

As far as the other issue, kind of the twin pillar coming up here, privacy and what people worry about is a different thing. It is going on a different track intellectually and I think it is probably going to take a different type of regulatory approach to get to it. So I would suggest, although I think what you have written, Marjorie, certainly gives some flexibility to do that.

I think we would better off starting at the beginning recognizing that and saying that there should be two different types and going at it and then what flows from there flows from there.

DR. SHAPIRO: Thank you.

Other comments?

Alex, I am sorry.

PROFESSOR CAPRON: I wanted to go back to this point that Steve has pointed us to on the language on page 34 about identifiable. And I guess I understand the situation described in the paragraph beginning -- the main paragraph there beginning "however" slightly differently and I need Marjorie and others to clarify this for me.

What this seems to say is the fact that research is conducted under a federal confidentiality protection means that the conclusions we drew about coded data being identifiable do not apply and as I understand that federal confidentiality protection, it simply says that if an attempt is made to subpoena or force the release in court or otherwise of information gathered by a researcher who has received this protection, the federal protection trumps whatever state process or federal court, any judicial process that would allow someone to gain access under that subpoena or the force of testimony.

Now that is only one, and I would say relatively minor consideration for the kinds of reasons that led us to conclude that coded data, even well coded data, remains identifiable. It is possible in any of those circumstances for people to put two and two together basically and we were just concerned that if you operated under some kind of

relaxed standard on the thought that because it is coded it is not identifiable you were making a category mistake, which we did not think should be made.

And I do not see how having that federal confidentiality protection changes that other than it says someone else cannot force you through legal process to disclose that but all the other reasons that people can put the data together and remember what we were concerned about, which was the temptation to do that for what people thought of as beneficent purposes but which they had not gone through a process which would have anticipated that and said that is okay here.

That is to say I develop information and, oh, gee, I really think it would be so good to be able to go back to those people and tell them this information, break the code for me so we can do that, you know, and I persuade you that is a good idea so we break the code and suddenly people are getting information which they had no idea was being collected about them because it had gone through a process that assumed they did not have to have consent because it was not identifiable.

We just said that is wrong. If you -- if that possibility exists you ought to go through a process which takes that into account and weighs the factors involved in advance. This federal

confidentiality stuff does not seem to me it is relevant at all to undermining and being a however to our reading.

Now others may take a -- others have taken -- I think OPRR and I guess OHRP take a different view on identifiable. I think they are wrong but this does not show that they are right.

DR. SPEERS: I would like to just clarify what Alex said. Under the current federal regulations there is the possibility for research to be exempt if it is covered -- if --

PROFESSOR CAPRON: Yes.

DR. SPEERS: If there is a federal statute --

PROFESSOR CAPRON: Yes, but that does not seem like it is a however to our recommendation. It is an existing thing that is inconsistent with the conclusion which we reached and which I would continue to defend. I mean, we are back to the sort of -- how do you put together our two reports type thing. I do not think we should retreat from that. We can note that existing interpretation differs from us and ought to be corrected to take into account the better reasoning we used in that document to make it consistent.

DR. SPEERS: Let me ask the question --

PROFESSOR CAPRON: Because this does not address what we were talking about. This addresses a

very different problem.

DR. SPEERS: But these two examples here, in both cases what we are talking about is where the data are already existing, they have been collected. One party has the data and that party gives the data to another party. And we are talking about whether that second party is engaged in human participants research.

PROFESSOR CAPRON: And if the data are given in a way which does not involve coding linked to their original source, the answer would be no. But if it involves coding or if it involves actual identifiers, the answer is, yes, it is human subjects research. And then we are back to the same issue that Bernie raised and Steve raised and Jim addressed, which is, well, once it is, that does not end the question. That then says, now, how should that particular type of research with its particular type of risks be reviewed and what requirements for consent and et cetera, et cetera, ought to attend that but it is research that involves human beings who are identifiable.

DR. SHAPIRO: Larry?

DR. MIIKE: Yes. The way -- it does not make sense to say this is a definition of human subjects research but, however -- I am agreeing with you, Alex -- however, there are certain instances where we are going to not define it as human subjects

research. It just -- so I do not agree with the OHRP and I agree with the HBM report that we had. Is that once having defined human subjects research broadly one can make exceptions to it and that is the way they should have gone about it, rather than saying -- it is not in the definition. They should say it is the definition but there are reasonable exceptions to it.

And I think that is the way we go because if we read the text here and then we read the recommendation, without the text in there you would have thought that that -- that these coded samples used by somebody else without being able to identify about somebody else having the repository, having it, we would have thought that that would have fallen outside the definition but there is no way to know that without having to go back and forth about this.

Do you understand what I am saying? I mean, because if you look at the current recommendation as written, one would say that, oh, you know, it is coded. So it is human subjects research but then we go to the text and say, oh, but in this particular case it is not. So it just does not make sense just logically to build exceptions to the definition. You should have exceptions to what is covered.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: So, Alex, I agree with you. I was not suggesting that these statements support or

whatever. They are just -- it was the striking fact that we were not told this back when we made the report and I agree with you that the statement in this report starting midway through line 25, NBAC supports the OHRP interpretation, is false.

PROFESSOR CAPRON: That is right.

DR. MIIKE: Right.

MR. HOLTZMAN: The HBM disagrees with that interpretation.

PROFESSOR CAPRON: Correct.

MR. HOLTZMAN: Now again just to remind us without getting into the old fight, there were sort of three different levels, right. The first is, is a human subject in play. The second was if a human subject is in play is the activity exempt. And if a human subject is in play and it is not exempt, can you nevertheless waive consent and under what conditions. But the last -- the first two that you never went to the -- on the first, it is not human subjects, you never went to the IRB. The second is effectively you went to the IRB and they could tell you it was exempt. The third you went to the IRB and now the question was --

PROFESSOR CAPRON: What do we do with it?

MR. HOLTZMAN: -- what do we do with it, right. And so that is where we -- so it is the playing through the consequences. So again whether we lump or split, all right, I just think that -- and

again we can have a respectful disagreement of the role of autonomy but I would advocate that there be an appropriate kind of review of the confidentiality issues by a suitable kind of review body who is focused on those kinds of issues as opposed to the classic ethics/bioethics one on one consent issues.

DR. SHAPIRO: I understand the issue. I think the issue that Steve, I guess, and others -- I cannot remember the pedigree of what all these ideas are here so I do not want to either assign blame or credit where it is not deserved, but the -- I think it is in the view of the Commission, certainly my view, that we ought not to change the position we took on this issue in the biological materials report.

But Steve has raised what I think is an interesting issue that is for what he has classified as noninterventional, whatever we get it -- talk about it in the end.

Are we fooling ourselves by letting the IRB review this for the risks -- the particular risks that are involved in these cases? And the IRB being -- I think what you were suggesting, Steve -- an inappropriate place to provide that protection and so what one might consider if I have understood your thinking on this is go all the way down the line just as you have just indicated and we say, oh, yes, there are some protections needed here for this coded but

identifiable -- these coded data, we need the right kind of people to provide the right kind of protections.

MR. HOLTZMAN: So let me tell you there is two ways to think about it and I am torn on this, all right. One way, if you say to yourself human subjects are really not in play here, I do not have to worry about that, I do not have to worry about the quality of the research in one sense, all I have to worry about is do I have a good coding system, do I have the right kind of confidentialities in play and, if so, anything goes. Then the IRB as we classically think of IRBs is not involved at all.

But there is another sense in which we say, well, weren't IRBs constituted to put into the pans of the balance the risk to the subject versus the value of that kind of research and there is a -- and that weighing comes back in because there is always the possibility that the coding system will fail and so there has to be some sort of question about the quality of the research and that does fall back into the purview -- part of the purview of what we ask of an IRB, all right, more or less. And that is what I struggle with, with how -- I do not know if you can simply bifurcate the tracks.

DR. SHAPIRO: Bernie, then Larry.

DR. LO: For this type of noninterventional research it seems to me that there are a couple of

issues. One is the issue of what is the risk and primarily what is the likelihood that confidentiality will be breached. And that I have been arguing requires a lot of technical expertise which IRB members may or may not have depending on their background.

At some point there is a value judgment made as to that risk may be very small but it is not zero and there are a lot of people involved here. You are dealing with hundreds and maybe thousands, and if you are dealing with the whole Medicare database it is millions of people. So that there is a flaw in the system even though there is a very low probability, there is a lot of data on a lot of people. And so you have got to weigh the kind of level of protection versus the way that applies versus the consequences of an unlikely breach of confidentiality that happens -- this is where I disagree with Steve's first option -- versus the value of the research.

You can get away from the -- if the IRB is a mechanism for weighing and balancing benefits and risks then I think this falls in their bailiwick provided you sort of have a broad view of risk that is very different from the notion of physical risk that IRBs are most comfortable with.

And also I think the other thing is that to the extent that the IRBs think that informed consent is a protection against risk that is not an issue

here.

DR. SHAPIRO: Okay. I have Larry and then Alex.

DR. MIIKE: I agree with Bernie in the sense that I do not think the first option that Steve posited and which we have discussed, which is a separate track would make any sense in a systems-wide approach. And as far as the IRB having primary jurisdiction, we have already said in many instances in areas in which the IRB may not have any particular expertise they should bring that in. We have talked about that in the cognitively impaired report. We have talked about areas where in AIDS research -- we have talked about particular communities and things.

So it is quite easy to have a recommendation, you know, that says in areas such as this that the IRB should rely on other expert bodies or constitute something that would take a look at this.

It does not make sense to me to pull out certain things and say, oh, it should go down a separate track, which also takes us away from our primary responsibility and we should not be making recommendations in some other field.

One last thing is that -- just going back to recommendation 2.3. Even though I know Marjorie has tried to combine the definition of research and human subjects, in practice you have still got to define

both of them. So it is really just a combined -- it is just basically combining two things in one recommendation.

And it would be clearer if we have two parts to these bullets. One should have -- because obviously one is looking at research and one is looking at human participants.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: I will surprise Larry by saying that I, indeed, very much agree with his point about not having separate tracks. The IRB at Mathematica or at the RAND Corporation or at a lot of other places never looks at any physical research risks at all and probably only looks at the risks of gathering data from various sources and so forth and so on.

So the notion that all IRBs only do one thing, I think, is wrong. The notion that Larry emphasizes that should be a general principle is that IRBs that are looking at a category of research should be constituted in a way that makes them able to give competent review of that research and again an accreditation process can look at that and whether the IRB has subcommittees or many universities have several IRBs, one that does their social science research and one that does their biomedical research. It is not at all unusual.

So there are all sorts of ways of addressing

this and I also do not think we should be talking about a different track but rather emphasizing as we did in the reports that Larry mentions the notion of IRBs either on a regular or ad hoc basis having the capabilities to look at categories of research.

DR. SHAPIRO: Is that Alta? Is she coming or leaving? Maybe she just hung up on us.

Any other comments regarding this? We are obviously going to have to --

PROFESSOR CAPRON: Are we going to look at anything else in 2?

DR. SHAPIRO: Yes, I hope so. No, let's look at some other things in 2.

Marjorie, is there anything you have particularly in mind in 2 that you would like us to comment on or would you like us just to take up comments Commissioners have?

DR. SPEERS: Right.

DR. SHAPIRO: Okay. Other comments on recommendation 2 or aspects of chapter 2?

Alex?

PROFESSOR CAPRON: I would suggest that we separate out, Marjorie, the first sentence of 2 from the rest of -- the notion of having legislation that mandates all research be covered under federal regulations regarding funding is a very major conclusion. It is something we have already concluded but it was concluded more or less as an

assumption back in the cloning report. We announced that that was what our view was but we did not have that as a part of a report and I think that should stand on its own.

Then the second recommendation is that to oversee all federal departments and all this other research there should be an office. I think in line with Jim's comment about the name of this report, I would also say that I think that that -- the name that we are giving to this is almost certain not to survive just on the argument that it does not say human in here anywhere and there are a lot of other research ethics issues, including what is sometimes called research integrity issues but what are thought of as research ethics questions.

And then just the whole question of the ethics of research in terms of is this a category of research that ought to be undertaken. It is an ethical issue. Should research -- you know, Einstein had views about certain kinds of research on the construction of nuclear weapons and the like. That was an ethical stance and it was about research. It just is too broad and all encompassing.

I think we would do better to come up with a title that is not going to be immediately subject to revision by somebody because it leaves out the important characteristic of research with human subjects or human beings and their protection but I

do not have a snappy -- I thought that one of -- whatever John Fletcher suggested had a better ring to it but I do not actually remember what it was.

DR. SHAPIRO: Carol?

DR. GREIDER: I just wanted to agree with Alex. I also felt that the title really should have the word "human" in it. It is not just research ethics. And one suggestion might be to keep the acronym NORE but NOHR, the National Office of Human Research or something like that.

PROFESSOR CAPRON: The Swedish spelling.

DR. SHAPIRO: That is right. Scandinavian approach.

Other comments regarding -- other recommendations to 2 or other aspects of chapter 2 or issues or statements made in chapter 2 that people have any concerns about?

If not, we will take a break and then in ten minutes go on. Thank you.

(Whereupon, a break was taken.)

DISCUSSION: CHAPTER 4, "THE LOCAL OVERSIGHT SYSTEM: INSTITUTIONS AND INSTITUTIONAL REVIEW BOARDS

DR. SHAPIRO: Colleagues, for those of you who like lots of recommendations and, more than that, lots of long recommendations, chapter 4 is for you.

This is -- for those criteria we have really hit the jackpot here.

But in any case without making any snide -- further snide comments about this, we do have a long series of recommendations here. Many of them, I think, they have -- of course, the ones we have before us have been redrafted some to meet the comments that many of you have sent in. So I think we ought to just take a look at the recommendations in 4.1 and see what comments people have and then, of course, also deal with comments with respect to the text for those of you that have some comments motivated that way.

Marjorie, is there anything you want to say by way of beginning this or should we just go directly to the recommendations and just deal with them one by one?

DR. SPEERS: I would suggest just dealing with the recommendations.

DR. SHAPIRO: All right. Let's take a look at them. We will just go at them chronologically here and move back and forth as we may find connections that are important to us.

What about recommendation 4.1? That is really regarding education and competency. Any comments or questions regarding recommendation 4.1?

PROFESSOR CAPRON: Marjorie, I am trying to find it but later on there is a requirement that as part of the accreditation processes, 4.14 --

DR. SPEERS: Yes, I believe that --

PROFESSOR CAPRON: -- that -- where is it? I am not sure it is 4.14. That is what I was --

DR. SPEERS: It is either 4.14 or 4.15 depending on what you are going to say.

PROFESSOR CAPRON: Well --

(Laughter.)

DR. SHAPIRO: And then we have another one --

PROFESSOR CAPRON: Okay. 4.15 as part of the accreditation process institutions must ensure certification of their IRB and staff. And in a way that is somewhat duplicative of 4.1, isn't it? I mean, what -- oh, at least it is not entirely clear if you look at the two of these if the successful completion of educational programs and demonstrated competency as to the IRB members and staff, not as to the investigators, which is not covered by 4.15, I guess.

Is that the equivalent of certification or is that what certification is supposed to show and, if so, it does not become a should ensure. It rather -- in order to carry out research they have to have an accredited IRB and in order to have an accredited IRB they have to have certified staff and IRB members. Am I reading that wrong?

I just think we ought to put these recommendations into order in some way.

DR. SPEERS: Yes, actually that is a good

point. I think you are right that if we require investigators and IRBs to be certified then recommendation 4.1, it really is -- could be subsumed under that recommendation related to certification.

PROFESSOR CAPRON: Or at least related to it.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: So let me try to get clear on what we are recommending. And let me for the moment use the word "accreditation" as something which applies to bodies of individuals as opposed to an individual and certification applies to individuals.

So among the bodies with respect to whom we could be looking for certification are IRBs, institutions that perform research and institutions that sponsor research. Right. With respect to --

PROFESSOR CAPRON: You said "certification."

MR. HOLTZMAN: With respect to accreditation.

PROFESSOR CAPRON: Accreditation.

MR. HOLTZMAN: Sponsors, institutions performing research and IRBs as regulatory bodies to speak of research, and certification could apply to IRB members, investigators and those that -- sponsors -- who oversee the investigators even if they do not investigate themselves.

PROFESSOR CAPRON: And IRB staff.

MR. HOLTZMAN: IRB/IRB staff, okay. So I almost would find it useful to write all those down and say which are we recommending.

DR. MIIKE: I do not think we are doing sponsors.

MR. HOLTZMAN: Right.

DR. SHAPIRO: Which would you like to recommend?

MR. HOLTZMAN: I actually would recommend all.

DR. SHAPIRO: Okay. Any other --

MR. HOLTZMAN: And Larry said to me we are not doing sponsors, and I actually think we should do sponsors and I do think we should be -- there should be certified individuals at the sponsors, including companies.

DR. SHAPIRO: Okay.

PROFESSOR CAPRON: Could we have that in blood?

DR. SHAPIRO: The blood comes later, yes.

(Laughter.)

MR. HOLTZMAN: I want the medical record --

DR. SHAPIRO: That is right.

Other comments on that? I mean, I think we should focus for a moment on Steve's partially rhetorical question of who do we mean to be certifying here. Put accreditation aside for a moment. We are now talking about individuals and

Steve has suggested really IRB members, investigator, staff who are participating in research and so on, and in addition to all that those representatives of the sponsors who are involved in oversight of any particular research project. That is how I understood you.

Bernie?

DR. LO: I very strongly support the suggestion that this should be sort of a very broad mandate. However, I would want to see something that talks about the -- both the training and the accreditation and oversight have to be appropriate to the type of research being done. I mean, right now what is happening is less than optimal. People are getting the paper certification and they are exposing themselves to things -- to ideas that have no relevance to the type of research they are doing.

So the NIH put up on the web its training program for certifying investigators. A lot of people do it because it is easy. It is there. It is totally irrelevant to 98 percent of research. It is for people who run a lab, that does samples on -- does tests on samples other people send them and the lesson is you are doing human subjects research and you need to send this to the IRB.

I have people at my institution that take that course and think they have past their educational requirement and been certified and they

know nothing about informed consent and all the other issues that are really key to the type of research they are doing.

So I think if the education and certification are not well done and pertinent, this whole requirement falls apart and I think we have already seen some evidence that it may not work as well as was hoped.

DR. SHAPIRO: Larry?

DR. MIIKE: I want to combine two things. One is that I thought recommendations 1 and 2 and then the later ones on accreditation and certification should be combined but I understand that the first two are really exhortations for education, et cetera. But I want to combine that comment with my disagreement about including everybody in the certification and accreditation process.

I think it is one thing to say that representatives of sponsors and of institutions who are not IRB members or a part of the investigative team should know more about the ethics. That is a separate issue to me from whether they should be certified as being competent in those fields.

So I would talk about -- I would recommend -- I would support certification of people directly involved in the research and directly involved in the oversight of research with a more general education

for those tangentially involved.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: Two comments. One is I think we ought to think how our recommendations differ from the present situation and my understanding is that at present what is in recommendation 4.1 is a part of the current recently promulgated NIH expectations.

In order to submit a research proposal you have to have gone through an educational program. And this suggests that it -- as is true, is institution based. That is to say your own institution is usually the one that does it. I was not familiar with people going to take that NIH one. I am sure that if it has the problems you described, it really is not a suitable substitute.

Where we differ is that in 4.15 we suggest that organizations with expertise in certification and research ethics offer certification programs and at the moment institutions, the research institutions themselves, universities and so forth, as I understand. They base -- I mean, we at USC did. We put on an educational program. Everybody who wanted to be a researcher, IRB member, came to that and when they were done they took a test and if they passed the test they got certified. And we certified them.

And what this says is the education may occur or ought to occur at each institution but the

certification ought to be independent of that. I just want to underline that we, in effect, are moving the ball forward there. That is a real difference and we should be aware of it.

The other question is the one that Larry addressed, I think, in some disagreement to what Steve was saying. But I thought what you said at first, Larry, would lead to a different conclusion so maybe I misunderstood what you were saying.

Rather than assuming that there is only one kind of certification, wouldn't it be appropriate for the person at a sponsor, whether it is NIH, some granting agency there who is overseeing the passing out of the money, or if it is at a company where they have a role as sponsor and under the FDA regulations they have very specific roles as sponsors, to be trained in and certified for that role even if they would not be certified as an IRB -- as expert in IRB review or as expert in and competent to be a researcher.

They have responsibilities and right now, I suspect, in some companies it might be possible that a person is assigned to that role within the company of taking the sponsorship oversight role who does not have a lot of background just as it is true that, I believe, still today FDA inspectors can be assigned one day to check for the rat droppings at the tuna fish company and the next day to show up at a

university and look at their IRB. I mean, if you happen to be at a university that is near a tuna fish factory.

(Laughter.)

DR. MIIKE: Just a quick response is that what I am saying is that for -- I can agree that people at NIH who oversee the grants program or, you know, whatever, and those in the industry that also oversee external ones should be more knowledgeable about it and that is why I am talking about educational courses directed at them. I do not see the rationale for their actually being certified. I do not know what you would certify them for and I think that as long as there is education and greater knowledge in what is at stake here, I do not think we need a certification program for those people.

PROFESSOR CAPRON: Well, as a university professor, I am used to situations in which people go to courses and go to classes but at the end I want to know what they have learned and so the certification is simply a demonstration that whatever the reason you were going to an educational program you learned what it was trying to teach you.

And I would simply suggest in line with what I took to be the drift of what you were saying that that does not have to be uniform because the roles are different but if there is a process of an assessment and you have shown the baseline of

competency, you understand what the tasks are and how they are done correctly, then you are ready to assume that role, and until then, whether it is being a sponsor of this kind of research or an overseer of nuclear technology or whatever, if there is something you should have learned, I want to know that you got it.

DR. MIIKE: But in a greater scheme of things if we take such a shotgun approach that everybody involved in the research enterprise must not only be knowledgeable but certified, I think we are doomed to failure about people taking us seriously and I think in practice what will end up is still a system where IRB members may be certified, researchers may be certified, but I doubt very much that there are going to be grants overseers at NIH who are going to have to go through a certification program or industry reps are going to have to go through that.

I think it dilutes the importance of a certification recommendation.

DR. SHAPIRO: On this issue we are discussing I really have two questions. First of all, I want to turn back to the point that Alex made a few moments ago regarding recommendation 4.15, I think it was, where we talk about organizations with expertise in certification. And I am always sensitive to issues when we are starting new

organizations because that is a hard thing to do and often an unnecessary thing to do.

But is it the view of the Commission that performers of research have sufficient conflicts of whatever so that they, themselves, could not be the certifying agency? I just want to clarify what the Commission thinks of this issue.

Carol?

DR. GREIDER : What do you mean by performers of research? Do you mean an institution?

DR. SHAPIRO: I mean universities, for example, or whoever -- whatever other institutions where research is performed, industry, other places.

Bernie?

DR. LO: Yes. Since I teach one of these courses I am very sympathetic to Alex's position that it is one thing to actually put your body in front of the teacher and it is another thing to actually learn the material.

DR. SHAPIRO: Yes.

DR. LO: I think that if it is like a medical CME where you sort of sign up the first hour -- that is a shadow requirement. I think there is an ambiguity in certification and I think to expect people to sort of do the equivalent of passing the boards in medicine, sort of going to a three hour test in another city that is multiple choice is probably over kill.

I do not personally see a problem with an institution saying figure out a way of ascertaining whether your investigators and the key people in your contracts and grants office or your IRB really know this stuff, we will figure out -- we will trust you to do that. We will check up on you but you can do that all internally.

I mean, what we are heading for, I think what Alex said, is we teach a course. It is a real course. Someone does not like it, they can look at my exam, they can look at the grading things and how I grade it, and they can say this is a Mickey Mouse course or it is an okay course. But that is very different than forcing each individual to go to something like the college boards or the national board of medical examiners, which is just a much bigger deal and much more cumbersome, and I am not sure is the right direction.

DR. SHAPIRO: Arturo and then Alex.

DR. BRITO: First, to answer the question directly about the institutions themselves doing the certification process, I think you are going to run into the same problems that you do right now with the same concerns about conflicts of interest that you have with the institutions having their own IRBs.

I agree -- I think I am in agreement, if I understand and am correct, with Alex and Bernie that there needs to be some formal certification process

that is not at a level of passing your boards but I think it has to be higher than something at the level of CME credits, et cetera, continuing medical education credits or whatever fits the person's profession.

But it has to be higher than that to be taken seriously because just my own experience with things such as domestic violence, requirements as a clinician, and I know a lot of people do not take these as seriously as they should because it is very simple to show up for an hour every two years and take -- there is not even a test for it, et cetera.

So there has to be something at a higher level. I am not sure where or when and how you are going -- but it has to be something that is standardized across the board, across universities and institutions and pharmaceutical companies.

But then what Larry is saying, I also have some concerns with, and I think not everybody needs to do this. I think the people, the key people here are to be certified -- certified, not accredited -- are the principal investigators at minimum. I think those people definitely need to be. And it almost will create a sense of, well, to be a PI on a research protocol, to be taken a little bit more seriously, you have to go through the certification process beyond the CME level and it will be taken a little bit seriously. Something that I think that

will be valued a little bit more.

But once you get into having everybody that is involved in the research then it kind of gets watered down so to speak and it is not taken as seriously so I think Larry's comments are very important.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: I am not sure that we are -- I know we do not want to create huge new organizations and I am not sure that anything we are saying here lends itself to that result but we have to be clear about it.

Certainly the expectation from this national office should be that if you are going to certify people as competent you should have a means of assessing them that will, indeed, assess that competency.

DR. SHAPIRO: I agree.

PROFESSOR CAPRON: If you are the AAMC, the Association of American Medical Colleges, with outreach to investigators basically at every institution, and you set up such a program and submitted your program of evaluation to that group, what we should provide is that the office has standards for determining whether or not a process of certification is enough. And that could be a web-based exam that you take after you have taken a locally provided educational program which -- or,

one, you have gone to a meeting of PRIM&R or something.

I mean, in other words, lots of people will be in a position at your own institution and otherwise of handing you a certificate that says, yes, you came for six hours of lectures and discussion, now you are ready to take the test and then you just go on to the web. I do not think this is excessively burdensome.

The only additional thought would be maybe an aspect of being accredited as a research institution should be that you have the ability to certify and again part of accreditation -- you can have accreditation with and without that ability if you choose to go through the process and develop your own method of assessment.

Again certain research institutions may think the kind of research we do is peculiar enough that we actually -- to do a good job -- want to make sure our investigators know things that might not be a general test so we want to certify them. We turn in our evaluation standards and the office says, yes, those are good, your scoring standards are good, you method of evaluation is good.

If someone passes your test and is certified by you that is okay and because of the way you are doing it, the conflict of interest problem is not insuperable. I mean, after all, we do allow

universities to do all sorts of other forms of evaluation of people and turn in the evaluation they have done, which counts for all sorts of things.

You can sit for national exams to become a licensed doctor based upon your university saying you have gone to the courses and have passed them and we do not say that is a conflict of interest because you are paying tuition that they are just going to give you your certificate.

(Simultaneous discussion.)

DR. BRITO: Right, a combination of the two.

PROFESSOR CAPRON: You cannot sit for the board without the work, can you?

DR. BRITO: No, of course not.

PROFESSOR CAPRON: I know you cannot skip to the boards without law school.

DR. BRITO: No, you cannot skip the years of residency and medical school, unfortunately, and go right to the boards.

PROFESSOR CAPRON: Exactly.

DR. BRITO: Unfortunately, right.

PROFESSOR CAPRON: Right.

DR. BRITO: But basically -- no, if you stand --

PROFESSOR CAPRON: It is a combination. So it seems to me that we could say that the accreditation process would allow a research organization to become a certifier of its own staff.

DR. SHAPIRO: My own sense is that we should allow some flexibility here. I mean, along the lines you suggested. I certainly believe that these things have to be tested. It is not just, as someone has said, CME -- and I hope there is nobody in the audience who developed the CME courses but anyhow, Bill, you are next.

MR. OLDAKER: Alex actually said most of what I was going to say but I think certification is the method by which someone has control over whether the person is actually competent or later found incompetent and the ability to reject certification or take it away is an important thing.

So, you know, as long as there is a centralized process that basically says whoever it is can get the license or get permission to issue the certification, I think that is all you need. It could be any type of institution, whether it be a professional organization or a university, and then you have to live up to whatever the centralized standards are.

And I agree that also it may not have to be anyone other than the principal investigator and possibly the chairman of the IRB but you want to have whoever the responsible individuals are in both contexts be certified. If not, broader certification. I am not opposed to having all people who serve on IRBs being certified but, yes, I think

people just have to think through what is the level of the burden that the system will take.

DR. SHAPIRO: Could I ask a question regarding some of the points that Bill just made and have come up before from those of you who have more direct experience in the actual conduct of some of this research, and that is it is my casual observation, and I underline casual, that the actual carrying out of the research across, you know, any human subjects and so on at times gets far removed from the individual principal investigator. And what you rely on is that system of people who are not the principal investigator, nurses, other kinds of people who interact, take interviews, do all kinds of things, that they know what their obligations are in this respect.

And that leads me if there is some truth to what I am saying or some reality to what I am saying to say that certification ought to be something beyond the principal investigator who may be running many projects at once and quite removed from the actual implementation and I do not know if I have a good definition to offer right now but I am concerned. I really thought in my own coming in here today anyway that I could not think of a reason why, to put it in the university context, that everybody who participates in this project just has to go through some type of appropriate certification.

And it is not like this is, you know -- to put it -- it is not rocket science, to use a cliche, to do this but it is serious and I think everybody who participates in these could do it if asked but I want to really look for guidance from some of you who know more about how these projects are carried out.

Arturo and then Bernie.

Sorry, Trish.

PROFESSOR BACKLAR: You are absolutely right. In many cases the PI may be more an administrator than anything else for the research and certainly may never actually even know -- supposedly the PI is supposed to get informed consent from the subjects or participants because that really rarely happens.

And so I think that your point is very important. Perhaps one could make it the responsibility of the PI to educate the people that he is going to hire or she is going to hire. That would be one way of dealing with it but you would not know for sure in the same sense that if you make this apply the people who were going to work in a research protocol should have some training themselves.

DR. SHAPIRO: Arturo?

DR. BRITO: It is true that many other people other than the PI are involved and often more directly involved with the research participants but it is the responsibility of the PI to educate anyone

else that is getting informed consent, doing any part of the protocol to educate them and make sure. Now I understand this is often not done or not done adequately.

What I was saying earlier is that if you start with a certification process that says the PI must have this and you raise the bar to standards that require a certain amount of knowledge and a certain level of sophistication, and it will be taken much more seriously by people that are PIs and I think that because of that they will take much more seriously the responsibility of educating others and making sure that their components in the research protocols that they are involved in are done correctly.

If you start to educate everyone from all research assistants, all -- maybe co-investigators should also be in here, right. I mean, we have not defined who or not but everyone that does any small component of a research protocol. I think what is going to start happening is the certification process will be one that is less sophisticated and you are going to lower that bar, and you are also going to slow down efforts to get any research done to the point where it will become so impractical because you are going to have, for instance, a medical student that comes along and wants to be involved in a research protocol, how long will it take them to get

certification.

And I think what is key here is for the PI to take the responsibility and to understand what his or her responsibilities are to educate the others and make sure they are following their components.

DR. SHAPIRO: Just again a slight comment before I turn to Bernie and then Trish, there are, of course, lots of these self-administered courses, tests and so on up on the web now because I went and searched out some of these a couple of weeks ago.

Some of them in my judgement, I am not a good judge of this, are really quite effective and easily accessible to anyone working with patients, and these are people, all of whom -- virtually all of whom are educated to some extent and so on but I do not want to make that judgment. I mean, I have not studied it carefully enough but I mean I was really -- I have not seen the NIH one. I did not go through that and his comments -- Bernie's comments are undoubtedly correct he made a few moments ago.

But there are others out there which take you through all these things in a step by step procedure with feedback and so on, which at first blush looked effective. Now that is all I want to say. I am not competent to say more.

One of these things -- you can either -- one of these things was put out by a university on the West Coast, you can even identify yourself, in which

case your supervisor got feedback on how you did and so on and so forth or you could do it anonymously. I chose the latter.

(Laughter.)

DR. SHAPIRO: Bernie?

DR. LO: I wanted to remind us of sort of all the other things going on, on accreditation and certification, and sort of ask what is our unique role here because in a sense what we are doing here is getting into the details that whoever really designs the certification process is going to have to work through, and I am just wondering if that is really our best role.

Greg Koski's office has contracted with the IOM to do a huge study, the first part of which is to start to suggest criteria which can be used as the basis of accreditation and certification. And the second part is an 18 month study which really looks much more broadly at the oversight process.

That group which is just getting starting will be charged with tackling a lot of the details on a level, I think, much more detailed than we are going to be able to get to. What they are very much hoping this group can do is to sort of give them the big picture.

I mean, it is not a totally done deal that accreditation and certification are a desirable thing and maybe one of the things we should make sure is we

make the argument that this is important, essential, practical, feasible and the like, and that, you know, rather than trying to address details maybe what I hear us saying is that there has got to be flexibility. Not everyone needs the same levels of certification. We want to really test what people know and we are afraid of it sort of being watered down as has been the case with other sort of required educational endeavors.

I think some of that would be important to state and state very clearly, and I just am not sure where the best body -- just because we do not have the expertise and do not have the time to truly get down to this level to really point to the questions.

Now having said that I cannot help from sort of jumping in on the level of details. It is very easy to sort of have lots of different levels. I mean, the IRB certainly can require people other than the PI to be certified -- to be fully certified if the project is particularly sensitive or particularly novel.

So it seems to me if you are going to do gene therapy you better have every party who even, you know, is within 20 feet of the patient be fully certified probably two or three times just to make sure they know it all.

But, you know, my secretary, who types my manuscript is on the grant for two-and-a-half

percent, really does not need to go through the same sort of certification even anonymously that we are all going through.

Funding agencies can on their own require all the key personnel, as the NIH so picturesquely puts it, to be fully certified.

So there are lots of different options that can be put in and, you know, maybe we just have to say people will sort of work this out but what is happening now -- you know, there has been a backlash. I mean, everyone is supposed to be certified by the October 1 submission dates. That got pulled back and I think the sort of let's go for it and then, my gosh, it is a lot more complicated and what we put out there really is impractical and may be missing a point and does not take into account the sorts of issues we have just been talking about. It does more harm than good so I just wonder if we should sort of do the big picture and sort of leave it to someone else to work out the details.

DR. SHAPIRO: Trish, do you have another comment?

PROFESSOR BACKLAR: I actually think Bernie made a very good suggestion. I had wanted to say that I noticed that you had made a suggestion that colleges and universities, but specifically if you are going to do that one would ask schools of nursing, schools of social work, people -- those are

the kinds of people who are going -- often going to be involved in research protocols, sociology departments. If you are going to make a list, those are the -- one would want to think of the kinds of people, the kind of education people are going to get who are going to become involved in a research protocol.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: So I agree with Bernie about keeping it at the high level. I think recommending something with respect to sponsors is at a high level and I would strongly advocate we do that.

Now, Larry, I guess the way I think about it is the following: And now I am thinking specifically of private companies as sponsors.

I would like to see it be a competitive advantage for companies to be good at the ethics of research. Okay.

So my thought is that you should have someone in your organization -- remember most companies do not actually conduct the research. Your sponsor, your clinical investigator, your clinical development people do not actually do the research.

But I want a certified person in the company and maybe the company is accredited if it has a certified person to oversee the research which you are contracting out.

That is where I am coming from on it.

DR. MIIKE: But, Steve, to have a competitive advantage, you do not make it a requirement for all companies to do it. You let the companies decide.

MR. HOLTZMAN: No, you cannot conduct the research unless you have a certified person and unless -- and your certification has not been lost so you have a stake in maintaining good practices.

DR. SHAPIRO: Larry?

MR. HOLTZMAN: Do you want to talk about how to run a company?

(Laughter.)

DR. MIIKE: No, but I would advise you on the ethics.

DR. SHAPIRO: We will let you run, Steve, the local state health department.

DR. MIIKE: I think the underlying basis for our recommendation is that we want assurances that people understand the ethics of research. We want assurances that there is, to the extent reasonable possible, uniformity across all levels and that then we are getting into the disagreement about who exactly do we want those assurances from.

And I do not think we are going to resolve this issue about where Steve wants to go and where I want to go so --

MR. HOLTZMAN: So we will just go my way.

DR. MIIKE: -- we will just go Steve's way.

(Laughter.)

DR. MIIKE: But again as we were saying, we are not in a position to say exactly who because we are already differing among the research team about who should be doing what and both the mechanisms of accreditation and certification. So I guess the emphasis should be that accreditation -- I do not think we are differing that accreditation and certification are the processes that we would like to see in place and how and what exact combinations, et cetera, and who it applies to, I guess we are just going to have to leave that in a more general sense.

DR. SHAPIRO: Alex?

And I want to come back to the issue of accreditation in a minute.

PROFESSOR CAPRON: Okay. I always -- because of my past experience -- listen to these discussions with an ear to what it would be like to try to summarize them in the next draft and what I would expect to see. And there has been a lot of agreement with what Bernie said and I think I would be one who would be in that group of agreeing.

I would still expect to see recommendations in favor of a system that requires those people involved directly with the human research projects to be certified. I could see the major point of the text that surrounds that to be, as he put it, making the case for that rather than having a long

recommendation that spells out exactly how that would happen. And leave again to textual discussion these variations that we have talked about. But I would not see a discussion that simply talked about it and did not in the end make that the recommendation.

And I guess my own sense is with Steve that it ought -- that while we would recognize that there may be levels of certification, you are certified for levels one, two, three, four, whatever, that we do not have to spell that out but the recognition that there are different appropriate levels depending upon the risk of the research and what is involved, the type of the research, and the level of the person's involvement and responsibility within the research project.

But it should still be the case it seems to me to answer Arturo that where you recruit or get a volunteer, a medical student who says, "I would like to work in this research project," you say, "Well, before you do that there are certain techniques about how to apply this drug or run that machine that you need to be taught how to do and there are also some basics about how you interact with, how you protect the data from, how you get consent from, et cetera, subjects that you have to understand and you have to understand there is a framework within which, and to do this one thing this is how we teach you that and to do this other thing this is how you teach it."

And, as the chairman has said, perhaps the answer to the latter is there is a good two hour tutorial on the web that has a series of questions and you will be certified at level four if you pass it and everybody on this project has to be at least at a level four, and I actually as the PI am at level one because of what is involved, et cetera, et cetera.

But you -- it is not -- the fact that you have got a volunteer medical student and you do not want to discourage that person, one of the things you teach them is that there are ethical responsibilities you have to learn and they are serious, and that there is actually some substance to them just as there is learning the Krebs cycle or whatever.

DR. BRITO: Just for the record, there is absolutely no disagreement with that.

PROFESSOR CAPRON: Okay.

DR. SHAPIRO: The accreditation itself, which we have all been in favor of here, is of course one that I think can be very useful and even a very effective method for achieving certain objectives.

However, anyone -- I think most people who have had any experience with accrediting organizations know they have their own dynamic or accrediting systems and often in my judgment cannot be relied upon to ensure more than minimal levels of capacity in this area, which is not always a good

enough standard to get to. And, of course, we know from accreditation in other areas when accreditation is threatened to be withdrawn that is usually followed immediately by a lawsuit and a long period of time before anything really happens and, in fact, in most cases nothing happens at the end because it all becomes very difficult to resolve.

And so I have been trying to think in my own mind about whether there are additionally -- I am not in favor of accreditation -- whether there are additional ways in which ongoing compliance can somehow be monitored in ways that would be publicly accountable, whether that is by audit systems of one kind or another or perhaps other systems which people could develop or articulate. But I do not -- I think the reason I have raised audit so many times here, I know you are all sick of me raising that issue, is because it relies on sampling which means it does not rely on going in huge systems to which you would subject this.

And I am just trying to ask the question if any of you think that is something worth some further thought in this context.

Bernie?

DR. LO: I very much think it is in the context of we are starting a new system that is going to be hard to design at the onset. We probably in the beginning want to build in a whole lot of

flexibility, coupled with the ability to go back and see which of the many different approaches works best in which situations and which work less well in a lot of other situations.

So I am very -- I like very much the idea of not being prescriptive at the beginning and saying you have to pass this one sort of national standard but there is many ways of doing it. Right now, frankly, I do not think anybody knows other than just a general impression that seems like a good web course and this does not.

But we should allow a lot of different models to develop but then have a way of going back and assessing in some respect, and I think sampling and ongoing monitoring ought to be part of that process.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: I believe all the Commissioners know but I should also have on the record each time the subject comes up that I am a public member, Commissioner, of the Joint Commission on Accreditation of Health Care Organizations, and that organization does not do any accreditation of IRBs so there is no conflict but it does give me some perspective on the development of the current field of accreditation.

And I think the joint Commission has been one of those bodies that has been subject to

criticism for some of the things that the chair was hinting at, both as to the relevance and usefulness of some of the activities in which it engages and the pressure that exists for an organization to be accredited, and all that follows negatively from that.

I mean, you set up a system like that and you can back into some problems of setting a low level because the cost of not being accredited is so great it creates pressures, particularly in an organization that is, in effect, constituted of the organizations that it accredits.

So I think it is, however, important to recognize that today accreditation in that context involves a lot more use and increasing use of performance data, which can then customize the site visits, the surveys as they are called, and allow sampling. For example, in the Network Accreditation Program where a system is looked at, a sample of the office sites and their processes are looked at, not all of them, within a hospital and looking at a particular activity, selected examples are looked at and so forth.

And so I think it is possible to have an accreditation system that involves both auditing characteristics, self monitoring, that allows bench marks to be established, and one of the good things about that would be much more communication among

IRBs and the ability to look at one's performance on certain key indicia and say are we doing as good a job as others and, if not, what are we missing in terms of the quality of our continuing review, our monitoring of consent in appropriate categories and so forth.

I think that the difficulty here will not be getting some value out of the program if it is correctly designed. The real difficulty is going to be in designing the program and figuring out what standards you are looking for because when you think of certain activities that we are more familiar with in patient care and the like, it is a lot easier, it seems to me, to figure out what you are concerned about that a hospital ought to be able to do correctly than it is to know exactly what standards will differentiate well-functioning from less well-functioning IRBs.

And I think that one thing we could recognize, Marjorie, is that this may be an evolving process. That is to say initially the emphasis may be on the auditing and site visit functioning rather than immediately having a set of standards in place and, frankly, even in the established area, something like the Joint Commission, it often puts out standards for use that are not scored for several years to allow the field not only to adjust to the standard but to get feedback on what the standard

actually means from the surveyors and the scoring process as to what is a passing score and where you are going to have recommendations, mandatory or otherwise, for change depends upon the experience in the field.

I have a sense that this will be something which ought to be seen and where we can talk about it as something which is not going to be plunked down on day one as a fully developed system.

DR. SHAPIRO: There are a couple of Commissioners who want to speak but I would just make one comment. Again trying to stick to the bigger issues as opposed to the issues -- I mean, I am perfectly comfortable with the kind of system of accreditation that Alex described that has those kinds of characteristics in it but it makes a big difference to me that it has the kinds of characteristics you described because often many accreditations do not have those characteristics of adjustment of monitoring and so on. And so if those were a part of it, I, speaking for myself, would be quite satisfied.

Bernie, and then Larry.

DR. LO: As just sort of one -- as a person who was site visited by Alex's organization and has to help prepare for them, I think that one thing Alex -- the only thing I would add to what Alex said is that the standards for what is acceptable also

evolve. So the first year that attention to ethical issues in clinical care was on the JCAHO audit you just had to have something in place to show you were thinking about the problem.

The next cycle things had evolved where you actually had to show that you had set up some sort of process that patients could turn to for counsel and advice and decision making.

And the next cycle or the one after, they were actually much more substantive standards of you have to show that you make a real effort to implement advance directives, you have a way of calling in mediators, if needed, on tough cases.

And so I think if we look at this as something that is going to evolve over time, and I think with a lot of input from the people on the front lines, and I would include IRB members, researchers and participants in research to help shape these because I think it is only going to work if we try some things and figure out these things seem to work and these do not, and then go on to the next step and make it an iterative process.

Alex was saying that it is really a quality improvement model we are talking about. That is really where you start as long as you are committed to collecting data that has something to do with how well you are doing, looking at the data and changing your system to try and do better. And if we get that

in place that is much better than sort of having a really good system at the onset.

DR. SHAPIRO: Larry?

DR. MIIKE: On your initial question about audits and monitoring, I am assuming that there is still going to be a monitoring and perhaps a strengthened audit function out of whatever NORE becomes. And recommendations 4.5 through .7 sort of touch on that issue, although they are not key towards removing funds, et cetera.

So while at the same time the accreditation process can have these strengthening kinds of audit and monitoring functions, there is still a separate track out of the NORE office.

DR. SHAPIRO: That is a good point, yes.

PROFESSOR CAPRON: But, Larry, it does not have to be separate because I mean if that data is coming in on an annual basis, how many research projects, how many subjects, what experience with adverse events, what happened and so forth, that can inform the site visit process and people can be looking for particular things.

The other thing to comment about is that, of course, with the Joint Commission but not with many other accreditation processes there is a cadre of surveyors, some of whom are full-time, some of whom are part-time, and some of whom are intermittent. I think the model that appeals to me much more here is

the site visitors being principally drawn from ranks of active IRB members and staff at other institutions.

And you get people who would need training in how to be a surveyor or a site visitor but who bring to it their own first-hand familiarity with it and you get cross-fertilization in the process, and a general improvement as people learn from each other about practices that work well.

Also, the oversight board that this national office has. I mean, the equivalent to this Commission that would be the advisory board for the office, I think, is going to end up spending a good deal of its time getting reports on exactly this evolving process and how far along in the monitoring, auditing and accreditation we are in the way that Bernie describes, and when are we ready to push for the standard to be a little more exacting on a particular topic.

DR. SHAPIRO: Bill?

MR. OLDAKER: First a question, Alex. When you are saying that there would be people going out there, are we talking about in an audit type function? Would they actually write a report on the site that they were at which would, you know, be helpful or critical of that site? If that is so, then I think that probably would lay the groundwork for people to either improve or to feel that they got

a gold star, which I think is a good thing.

PROFESSOR CAPRON: Yes.

MR. OLDAKER: The other thing is I would think that, you know, what we are talking about is something -- what we are talking about here is these accreditation or certifications are going to be statutorily based and they are going to be something that at least is originally recognized as a function from the statute which will get delegated to the federal organization which will then, in fact, delegate authority down to whatever the accreditation or certification.

If that is so, there are ways, I think, Mr. Chairman, probably to avoid some of the litigiousness of those in setting it up and I realize an associational --

DR. SHAPIRO: That is a good point.

MR. OLDAKER: -- there is almost no bounds so people look at it and there is lots of questions. If it is statutorily based accreditation, I think there are probably ways to cut to the --

DR. SHAPIRO: That is a very helpful point. I agree.

PROFESSOR CAPRON: One of the characteristics of many accreditation systems -- I am not sure this is true in the university sphere -- is that there are competing accrediting organizations and, of course, in the area of hospitals and so forth

the question is are you getting your certificate of participation in Medicare directly from the government by having a state inspector come or are you choosing accreditation by an organization which has what is called deemed status, that is to say its program is felt to meet the federal requirements.

And when we talk about monitoring and auditing, I take that to be something that aims more towards the federal requirement itself. That is to say finally fulfilling the recommendations of the President's Commission that there be a database based upon this auditing process and monitoring that would allow us to know how many research projects are extant and how many subjects are involved in them of different types.

The accreditation process, though, may be one where you would do a deeming and say this organization and this and this and this can all offer you accreditation that meets the federal requirements and all of them have access to the relevant database so that they can do their survey or their site visit in a way which is attuned to the relevant facts of this organization, often trying to look for trends at the organization, and particularly if a trend indicates a problem area that needs special attention.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: If I heard you, Harold, I

think you were -- what -- the argument I would make for a certification/accreditation process and making it happen is one of the things we have heard is that the whole complexion of research is rapidly changing with new players and new actors, a lot more involvement of the private sector and whatnot.

And there are assumptions about illegitimacy, particularly when it is for profit. We have heard about the independence of for profit IRBs being slammed even though -- and what we are really talking about here in general is all research should be put on the same footing and judged in the same sorts of ways. And this is one way to just reset the clock and say let's define quality and measures of quality.

DR. SHAPIRO: I agree with that.

Bernie?

DR. LO: Two other points that I think we can call attention to. One, I think, builds on something that Bill said, which is the difference between providing incentives for people to want to get certified versus requiring it as a matter of legislation or regulation. I think groups like NIH and FDA, other organizations can do a lot to provide incentives for institutions and research teams applying for a grant to have higher levels and broader certification in their project than otherwise. And you can think of things like allowing

people sort of short cuts in the applications process, for example.

And, secondly, I think we should at some point acknowledge that there are costs to a certification. It costs time. It costs money. It is not clear where this is all going to come from. And we need to make sure at the end of the day that what we get out of it is worth what we put into it and I think it is an open question now as to whether that is going to happen. I think we should just be up front about it and say we would like to see this happen and it is up to the good will of the parties involved to really kind of get behind this.

I share something that -- concerns that Arturo raised. When you think about the number of -- as a physician, the number of things I am required to kind of be educated in, you know, domestic violence, cultural sensitivity, I do not think those programs have really done anything other than to say somebody thinks this is important but the level of education is so spotty that I do not think it really improves the quality of service in that dimension.

I think that people are very understandably cynical about yet another kind of requirement to be educated on something else.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: I want to raise a related issue that I think we just have to be aware of. I do

not think that this accreditation issue is going to be any problem for major research organizations. I think they are going to mostly accept it. They will be capable of meeting any reasonable accreditation requirement, particularly one that was a rolling requirement that gave them time to adjust as needed.

A major issue, and I think a perfectly appropriate issue, is that a lot of research now is taking place in individual physician's offices and it is often under contract research organizations' sponsorship. They get a contract from a drug company and they find the doctor's office and so forth. I think there is every reason to believe that some of that research is further away from the ethical standards that we would expect than research that occurs most of the time in universities to put it mildly.

And it seems to me that our -- we do not have a lot of experience with accrediting individual doctors' offices for anything now and it will be a task which we ought -- we are not going to figure out exactly how that is going to get done but I think we have to identify that as an issue that to the extent that sites are -- individual/sites as that sort, how it gets -- how they get accredited to be a participating site, whether the accreditation just goes to the contract research organization, which then has to engage in some kind of process itself to

make sure that those doctor's offices are suitable both in the ways in which subjects are recruited, the consent is gotten and disclosures are made and so forth. That will remain for NORE to take care of but I think we should flag that as a potential difficulty.

If it makes it more difficult to do some of that research, I frankly would not be that disturbed. That is to say if some of those doctors say I just am not going to go through that process, it is not worth the money I am being offered, maybe they are not places that the research should be going on but it will be -- it will raise some concerns in some quarters.

DR. MIIKE: But, Alex, individual doctors, I am assuming that the certification process would take care of the physicians as researchers and it is no different from JCAHO not accrediting doctor practices versus accrediting hospital settings as a place of care for medical services.

PROFESSOR CAPRON: But actually the Joint Commission is right on the cusp of accrediting doctors offices because of the amount of office based surgery, including that which involves conscious sedation that has now been pushed off into the doctors offices or for financial reasons doctors are now doing in their offices. So we are at the cusp of exactly this issue and you also then have the issue

of hospital owned physician practices which are, in effect, treated like other ambulatory sites within the hospital.

But I am saying knowing the difficulties that we face there, I am sure -- which are partly physician resistance to the notion of going through an accreditation process because they are not familiar with it. Some of that same resistance will come up and some people will say, "Well, you are saying to me if I do not do my research not at the University of California at San Francisco but at Dr. Jones' office some place down the street, his office also has to go through a process to be an accredited site. I will never get him to agree to that. You are cutting me off from that site, you know, community research is good," et cetera, et cetera.

And I think the answer may be, well, they are going to have to figure out how to deal with that tension but I would not -- I would not fail to mention it because it is going to be an issue. Nor would I say, well, if it is not the research institution itself then we should not worry about accreditation. I think we should worry about those sites and partly because I think we already have evidence that they are some of the more troubling sites. At least there have been examples of very troubling research.

DR. SHAPIRO: Bernie?

Steve, did you have your hand up?

Bernie?

DR. LO: Harold, I wanted to ask a sort of procedural question about how you wanted to use the rest of the afternoon for other recommendations than chapter 4.

DR. SHAPIRO: Yes. I want to get on them right now.

DR. LO: Can I nominate?

DR. SHAPIRO: Yes.

DR. LO: I mean, two issues I would like to have us discuss because they are such important and complicated issues are adverse event reporting and conflicts of interest. These are two of the issues that really spark the public interest in this and maybe just to start with 4.7 because it is a lower number.

A couple of things about that. First, this is one of those situations where we should be very careful to acknowledge that there are efforts already under way to kind of harmonize the adverse event reporting between, I guess, what is now OHRP and FDA.

Two issues that I would like to sort of see us highlight are first the role of data and safety monitoring boards in not only collecting adverse events but sort of what they do with that information and it seems to me a double edged sword.

On the one hand, my own experience with

DSMBs is that they are very, very well situated to really assess adverse events because they see the whole picture of what is going on in the trial. It is very difficult, I think, for an IRB that does not have access to all the other data that is coming in to really know what to make of, you know, one or two adverse events that cross their doorstep.

The other issue I think it would be very important to deal with, with regard to adverse events is the claim of some sponsors that they cannot report adverse events as required by law because it would violate -- it would breach their trade secrets and give away confidential information they need for their own product development.

I think there should be ways of masking the data so that the -- what is the essence of the trade secret is kept secret but the nature of the event -- the nature of the adverse event and the frequency of the adverse event and the severity of the adverse event is captured so that a pattern can be seen.

I think those are two issues where there is a lot of discussion going on and I think to the extent that we can help contribute to what is already an ongoing discussion while sort of supporting the general thrust to make all these different reporting systems work together would be very helpful.

DR. SHAPIRO: That is quite helpful. Are there any other comments on that particular issue

that Bernie just raised, namely for us to pay some attention to the role of the data safety and monitoring board, DSMB if that is the right initials, here and acknowledging and finding some way to deal with the proprietary concerns drug companies and others often have. I think it is important to note these and to deal with it.

PROFESSOR CAPRON: I would find it helpful to have testimony in a future meeting from some of the people from pharma or otherwise who are involved in this because as I understand the issue for them, what is proprietary is the very fact that a particular drug under study has had an adverse event. I mean, that has an impact on their proprietary interest in the drug and so the notion that you can "mask" something, while appealing, requires some further elaboration.

What is proprietary is your trial design and your indication. That is where you will have a proprietary advantage. If you have an adverse event related to the drug you are required to report it and if the FDA makes the judgment that with respect to someone else has a drug in trial or about to that has similar characteristics, they will go to that person and they will say, "We would like for you to make sure you do the following tests."

So if I am testing a drug of class X and someone else has a -- and I have had a serious

adverse event of the liver and they have not seen it, the drug -- the FDA will say to them we would like you to do more liver function tests, for example. Or if it is exactly the same chemical composition, they will stop them.

So there are ways of dealing with this because it is not the adverse event itself. We would object to them saying so and so is testing the following drug for thus and such and had a bad thing. Let's publish it all over the press.

PROFESSOR CAPRON: Yes.

MR. HOLTZMAN: Right, but if it is to protect the public --

PROFESSOR CAPRON: It may be that you have just given enough but I would like the report to reflect a sophisticated understanding --

MR. HOLTZMAN: I agree with that.

PROFESSOR CAPRON: -- of what the arguments are and just saying, you know, it is proprietary does not begin to get to it. And, also, to make sure that we are hearing from the hardest line, hard line on this, because a few of your comments a moment ago about, for example, certifying sponsors may mean that your name plate is not at the head table at BIO this year.

(Laughter.)

DR. SHAPIRO: Bernie, on the same issue?

DR. LO: Same issue.

DR. SHAPIRO: Okay.

DR. LO: I support Alex's suggestion that we sort of find out what the position is of the stakeholders here. I think Steve's example is a really good one because, see, I would argue that data and safety monitoring board can play a very key role there because what I have typically seen is when you see those first couple of events your antennae go up and you say let's go back and review all the other cases to make sure we have not missed subtle liver damage.

And then they usually say in this protocol let's go out and require more frequent monitoring of liver function tests or let's make sure that we have excluded people who are taking another drug or hepatitis or something else that is causing liver problems so that you can actually be much more efficient within a trial where there is no concern about breaching confidentiality really figure out is this a real association, a serious one or is it just sort of a fluke.

The difficulties come in when you start to get that threshold of should you warn other people using the drug and then I think you do have to have a regulatory body like the FDA step in and make that determination.

DR. SHAPIRO: Any other comments on this particular -- Bernie, I think you said you had a

second issue and 4.7 was the low number.

DR. LO: Well, conflicts of interest.

DR. SHAPIRO: Yes.

DR. LO: Which I think is just a real difficult complicated topic. Recommendation 4.12 is where we start to deal with it and I guess -- again I want to step back. This is an issue -- there are going to be zillions of conferences and symposium and panels just on conflicts of interest. SOROS Foundation is doing one and stuff. And again I am trying to think of what is our niche, what is our unique contribution to this debate.

And some of it really may be sort of the basics, you know, why are conflicts of interest particularly deleterious in a research setting? Because they destroy trust. Why is it that scientists, researchers, physicians tend to think they are different from all other professions that have very strict rules about conflicts of interest?

I mean, there is just a -- you know, it is really funny when you talk to doctors. They are offended that people should think there is a problem whereas they think they people in public service -- I mean, all of us have to fill out these forms and, you know, we cannot have someone pay our way to, you know, Denver to give a talk without prior approval.

So I think there is this sort of real -- let's get real guys, conflicts of interest are

serious and you have got to face up to it.

The institutional aspect of conflict of interest, I think, is a real bugaboo and I think has been under appreciated and, frankly, a lot of large research institutions have ducked the issue and maybe this is a place where we can be out front and say they are as important and as threatening to trust in the research fabric as the individual investigators.

And, secondly, recommendation 4.12 to me highlights a problem of how we respond to conflicts of interest. The federal response up to now has been disclosure and management of conflicts of interest. There also is a role for just flat out forbidding certain situations as posing too grave a threat of a conflict of interest and they are just flat out unacceptable. And, again, that is not part of the discussion here, whereas it is in every other profession that faces conflicts of interest.

So again I want to sort of step back from the details and sort of try and -- where is this whole discussion with regard to research? It is just way off base and I think those are three of the areas where we are just out in left field some place.

DR. SHAPIRO: On this conflict of interest -- Alta, hello.

PROFESSOR CHARO: Hi.

DR. SHAPIRO: On the conflict of interest I think you have identified it correctly, that is that

the typical response is disclosure plus management. Right, disclosure leads you -- gives you some way to manage what has been disclosed in ways that are appropriate.

And then prohibited is, I think, an important standard. Quite frankly, as I thought through this, I had a hard time deciding how to get to prohibited. When I think of financial conflicts of interest especially. That is I certainly understand there must be -- I can invent cases that are -- which I would feel, you know, these cases that are people are clearly prohibited but then I try to give an analytic judgment of those and I have had a hard time identifying them. Perhaps there are others here who could help out in this respect. I mean, I can identify examples. That is no problem. But a kind of analytic concept which would tell clearly an IRB what things are prohibited and, therefore, that investigation cannot go forward has been hard. But if anyone has some ideas on that, I would like to think that through.

DR. LO: One thing that we suggested in an article we just published is that in a clinical trial none of the investigators may hold stock or options or management positions in a company sponsoring the trial or manufacturing a product being tested.

So that if the amount of your personal compensation has a likelihood of varying depending on

whether the results of the trial are positive or negative, that is an unacceptable situation in that you never know whether a decision that can be criticized in retrospect was just the best judgment at the time or whether it was tainted by unconscious bias.

So I think there may be large areas like that where most people would say it is just not worth the risk and you can always turn it over to another colleague who does not have stock or options, has no ties to the company other than the percentage of time they are being paid for to do the grant, and let them do the Phase 2/3 clinical trial.

Even that as kind of a first step would be a big first step because you would say you cannot do it and we just looked at the ten leading NIH supported biomedical research institutions and only one had a policy that came close to that. Four -- six of them saw no problem in our policies with an investigator in a clinical trial holding stock and options and that just -- I do not think -- is not right for a whole lot of reasons.

DR. SHAPIRO: Other comments or questions?

I have to confess when I thought it through I shied away from that kind of prohibition. I understand its benefits. I really do. And you have to but there is a -- I always was stumbling on de minimums holdings, you know, how do I define holdings

if you have a mutual fund who owns some SmithKline or something else, does that mean you cannot -- there is a whole set of issues there which perhaps are certainly a level of detail we do not want to get into. I mean, I understand that.

So it would be a question of how we could articulate that in a way that would show some guidance to what kinds of things might -- you know, someone might want to consider for actual prohibitions.

PROFESSOR CAPRON: You are agreeing with the notion that the conflict of that sort --

DR. SHAPIRO: Yes.

PROFESSOR CAPRON: I mean --

DR. SHAPIRO: It is very troubling, right. I agree.

PROFESSOR CAPRON: -- research -- if you had a protocol, an agreement, which said that you will be paid based upon whether or not the data you turn in will lead to the successful --

DR. SHAPIRO: Well, that would be clear.

PROFESSOR CAPRON: -- licensing of this product.

DR. SHAPIRO: Yes. No, that I -- that was -- that is clear.

PROFESSOR CAPRON: And yet in an entrepreneurial closely held corporation situation where the researcher is a principle in the

corporation or a holder of any significant amount of stock --

DR. SHAPIRO: Right.

PROFESSOR CAPRON: -- that is what it is.

DR. SHAPIRO: That is right. In most cases that is quite clear.

PROFESSOR CAPRON: And so you are right that the attenuation of holding an amount proportionate to one's own other holdings in a publicly held corporation or in a mutual fund which holds stock in a public --

DR. SHAPIRO: Right.

PROFESSOR CAPRON: I mean, there is a level of attenuation in there.

DR. SHAPIRO: That is right.

Larry?

DR. MIIKE: Well, while we are on the subject then, if we are going to be trying to address this or at least discuss it, we should talk about institutional conflicts of interest, too, because that is clearly a bigger issue, right?

DR. SHAPIRO: Right.

Arturo?

DR. BRITO: I was just going to say something similar to that. My level of discomfort hearing what Bernie just said is that I am not sure it is unfair when you come to institutions and different kinds of conflicts of interest that are not

as directly financial or as obviously financial as those.

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: First, I apologize. I was in a meeting all this time and I only just got out.

DR. SHAPIRO: So were we.

PROFESSOR CHARO: I hope this is not going to be redundant but one of the background questions I have asked myself and I have not quite answered yet on conflict of interest is which particular goal we are trying to serve. There are two possible goals here. One is to actually make sure that people's decisions are not unduly influenced because we want to make sure that the substantive decision is appropriate.

A very different goal is to ensure that there is a perception that the decisions have not been unduly influenced, which would argue for a much more Draconian, one might even call it, set of rules about conflict of interest and it depends on whether you think the issue really is that wrong decisions are being made and people are being hurt or treated badly that should not be hurt or treated badly, or if on the other hand you think the real issue is maintaining public confidence in the system. Until I can decide for myself what the goal is, it is hard for me to evaluate the kinds of recommendations that

are appropriate.

DR. SHAPIRO: Bernie?

DR. LO: Yes, Alta, I think that is really an important point and I would suggest that they are really inseparable, that what the Gelsinger -- one of the lessons of the Gelsinger case may be that when you go back in retrospect and look at the protocol you can always find things that in hindsight you wish you had done differently.

The problem is that when a terrible adverse consequence happens for a research participant and you go back and look, it is very -- it is impossible to sort out whether the investigators are just doing the best job they could do at the time with imperfect information or whether subconsciously they were sort of really trying to push it through a little bit too quickly or trying to cut corners because of their very heavy personal and institutional financial stake in the matter. So I think the perception of trust and the adverse outcomes are very hard to separate out.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Isn't it the case and the irony, right, in that case is that the PI did not have a financial interest in the company? The clinical investigator did not, all right, but he worked for someone who did.

DR. SHAPIRO: In that case that is right.

DR. LO: But, also, the head of the lab who was the co-founder of the company, he only turned over to the subordinate who had no financial links the patient care decisions. He was still involved with the design of the project, which would include selection of subjects, whether you started with the asymptomatic adults or not. And in the assessment of what constituted an outcome and an adverse event so that he mainly said I do not want to be involved in the informed consent interactions and the patient care interactions but it seems to me that as the investigator there is a potential for bias and harm throughout the studies from the design to the data analysis phase, and not just when you are interacting with the subjects.

DR. SHAPIRO: I want to try to get the sense of the Commission on this conflict of interest issue, which is a very important set of issues. It has been pointed out that we have both the institutional conflict of interest and the individual conflict of interest. It is not easy to get a detailed set of recommendations but it is, I think, in my own mind not conceptually difficult to handle the individual conflicts of interests. You have to decide exactly what you want and exactly what you would insist on.

But nobody has made any suggestions so far regarding institutional conflicts of interest, namely that institutions may have a reason for wanting to do

-- wanting to participate in these kinds of activities, financial or otherwise, and yet they are the same people that are trying -- that in the end are responsible for approving or monitoring this research.

Alex?

PROFESSOR CAPRON: Well, there are two types of incentives here that might be conflicts and when we were talking about the payment for doing the research, Bernie suggested, well, that is not the conflict as to the individual researcher. The idea being if I were not doing this, I would be doing some other activity and it is not a contingent payment and it is not a conflict.

And yet in the context of the institution where we talk about the institution having a conflict or IRB members as professors at the institution or other staff at the institution and wanting the institution to do well, being willing to approve research, which maybe they ought not to or ought to redesign, and it is the notion that the institution gains finances and perhaps prestige from having a large research base. And there it is not the contingent payment, it is the direct payment.

And it seems to me that the kinds of rules that we could have vis-a-vis institutional ownership in the entrepreneurial side of things where it seems to me it is perfectly reasonable to say the

institution ought to be equally distanced from research that is going to take place there that its own portfolio should not suddenly be going up because it agreed to allow research to go on that was going to lead to something does not get to this more difficult question of whether the institutional bias towards research at all ought to be prohibited.

And I can only think that there are ways of protecting the body that is most directly involved, namely the IRB, from institutional pressure that may be about the only thing that we can do.

I mean, the notion that IRB members, particularly with the kind of diversity of membership that we are talking about, do not have their membership contingent upon the whim, as it were, or the directive of a person who is in charge of the research operation so that if I am sitting here voting against protocols or insisting that researchers redesign protocols, and they are going elsewhere to get their research done at a more lenient place and the research director says, "I want this guy off the IRB, you know, he is just a pain in the whatever and I do not want him around anymore," that should be illegitimate and there should be protection for the independence of the IRB members and the staff who are carrying out the function.

They should have -- there should be some protection there.

Again designing how that happens -- but I do not think there is any way we can keep the other from happening any more than the researcher who wants to do research at the cutting edge because it is going to lead to fame but not fortune. I mean, that is another motivation that drives people and we recognize it is an inherent conflict that is not something that you can prohibit.

DR. SHAPIRO: The question of whether institutions should think they have equity interest in these kinds of projects or with companies in which there are faculties engaged in research, how you should act depends very much on which meeting you are attending and which branch of government has called the meeting because this is widely encouraged for all kinds of reasons which make some sense, I have to say, in a certain kind of context. And then in another kind of context it raises the kind of difficulties we are just facing right now.

And I think institutions I speak to about this are just generally troubled by what kinds of policies they should have given these kind of conflicting pressures on that issue.

Steve?

MR. HOLTZMAN: I actually would like to see that -- even more spun out in our discussion of this because I am completely sympathetic to the notion that the IRB should not be getting pressure from the

top who is saying we want you to be perceived -- we want you to be perceived as a place that -- an institution that can get grants and is user friendly.

On the same token, I go in and negotiate with heads of health care systems and I say, you know, there has been a real problem dealing with your IRB. Not because I want them to be more lenient but I want them to be more efficient. And so they are bringing -- but how does it appear, right? Similarly, we have statements in here about it is really -- you know, and the tone of it, it is egregious that companies pay docs for patient accruals and give them bonuses for getting them quickly.

Well, we do. All right. Why do we? Because, in fact, you know, the single greatest obstacle to -- the single greatest cost in a clinical trial, and the slowest part of it, is patient accrual, all right. How do you incent people to do it efficiently? Not to do it unethically but to do it efficiently. And like Harold says, I sit in lots of other meetings about how do we use market mechanisms not to make people unethical but to make them more efficient.

So I think we need a little more sensitivity in the document that it is the -- the world has a lot of gray in it.

PROFESSOR CAPRON: If I might, would you

insist that your people who are incented in that way reveal that to the subjects? In other words, I want you to enroll and, by the way, if you do, I get $1,000 bonus today?

MR. HOLTZMAN: It would not have occurred to me to say that they say to the patient or to the subject, the research subject, that we are paid X amount per person that we accrue and so I would not be inclined to say that they would, therefore, have an obligation to say and if I accrue 100 in three months as opposed to in six months I get an extra $1,000, no, I would not see it as part of the disclosure.

DR. SHAPIRO: That is interesting. As I thought about these conflict of interests it seemed to me that the disclosure -- appropriate disclosure to participants is really quite important because we say in here -- I have forgotten which chapter and which place -- that the participants also have an obligation, right, to assess their own situation and protect themselves as best they can and they need information to do that.

And I have not -- I do not know precisely what question you were asking, Alex. I do not have an answer to that but it seems to me that in general participants are the appropriate -- ought to be fully aware of these financial conflicts or potential financial conflicts so they can make their own

judgments as to whether -- how to assess what they ought to do.

And you had a kind of second order derivative kind of system in here. The last little incentive you thought they did not need to know about but the first incentive they did.

MR. HOLTZMAN: No, I said they -- I was actually going back the other way. We certainly disclose that there is a company involved and there is financial interest in it, whatever you think of the Moore case, the one feature everyone agrees about in Moore is that there is a set of incentives in play that compromised the relationship of the doctor to the patient, and by extrapolation is the researcher to the subject.

DR. SHAPIRO: Right.

MR. HOLTZMAN: All right. Such as financial conflicts or the presence of a financial, and that is what Alex is asking a question about. Where does it -- where do you have to say it is out of the ordinary. People -- investigators are paid on a per patient basis. Does the world know that? I do not know. Should it be in general -- should everyone say in every consent, "Oh, by the way, you are in a clinical trial, we are going to pay you this much and I get paid to do this clinical trial." Now the rate per patient, should we get into that? I do not know, you know.

PROFESSOR CAPRON: If you announce that there is payment you at least invite the person to say, "Well, how much are you being paid?" If they do not know it, they would not think to ask that. You are just my doctor.

MR. HOLTZMAN: That is fine. And then, of course, if they ask for a cut, now of course you are improperly incenting them.

(Laughter.)

DR. SHAPIRO: That is a negotiation.

Bette and then Bernie?

MS. KRAMER: Well, actually I guess you just answered my question but I am sitting here thinking to myself, I have no idea how investigators are compensated and I guess a more interesting -- I mean, an equally interesting question to me is what is the incentive for investigators to become involved in an investigation? Is it the financial interest or -- I mean, you know, I know there are going to be as many answers to that as there are investigators but I would be interested to hear a short response from Steve.

MR. HOLTZMAN: It depends on the investigation.

DR. SHAPIRO: I think disclosure accomplishes a lot in this respect. That is to the participant. So my view is you just disclose these matters to the participant and they make their own

judgments about what they think about you and the protocol.

MS. KRAMER: Well, a follow up question. So is that the sole means by which an investigator is paid to run an investigation is the per participant enumeration?

MR. HOLTZMAN: That depends.

DR. SHAPIRO: It depends. The answer is no.

MR. HOLTZMAN: In general, no. I mean, because that is part of -- the investigator will be undertaking procedures with respect to the individual. It depends on the trial.

DR. SHAPIRO: Trish?

PROFESSOR BACKLAR: Well, of course, it may be clinicians who are cooperating with the PI and bringing people into the trial. Actually what I would like to talk about here because I cannot remember where in the document this was addressed and if we addressed it adequately, in the beginning we had some discussion about the IRB itself being independent of the institution and, in fact, I think it was Dr. Koski that said -- mentioned taking the -- I may have forgotten -- the "I" out of the IRB. And I am not really finding this in here. Is it because I have missed it or was it decided not to look at that, the possibility?

And I am looking also at Tom Murray's article on the New Zealand independent IRB and I do

not think we really addressed this. I do not think we did address this really in Utah, did we, to any extent? Of the independent IRB?

DR. SPEERS: We have not -- you are correct. We did not have any discussion per se of the independent or the noninstitutional IRBs. We added just a discussion on alternative models in other countries that we have in there.

PROFESSOR BACKLAR: So this is something that is no longer being considered?

DR. SPEERS: Well, I mean, we could add -- we can add something about the independent or the noninstitutional IRBs in the United States. We could add that. If you are asking us to add something about Dr. Koski's discussion about taking the "I" out of IRB, we would have to discuss with that office if that is still an issue that they are contemplating.

Is it the latter that you are asking me specifically?

PROFESSOR BACKLAR: Actually I was interested that we did not address this ourselves because I thought in the beginning of our discussion that it was an option that was in play and as I go through this I find that it is no longer in play and I am a little concerned because I actually thought it was very interesting and I would like to have discussed and thought about it.

DR. SHAPIRO: I just want to make sure what

you are interested in, Trish. The possibility that we might recommend that institutions -- it is already true that institutions do not have to have a local -- their own IRB but you are interested in whether we should require institutions not to use their own IRB.

PROFESSOR BACKLAR: Well, I was thinking more -- we had one meeting here in Washington where we had a number of people, somebody from Denmark and --

DR. SHAPIRO: Right.

PROFESSOR BACKLAR: -- I forget wherever else --

DR. SHAPIRO: Holmes.

PROFESSOR BACKLAR: -- and discussed how regional IRBs worked.

DR. SHAPIRO: Right.

PROFESSOR BACKLAR: And it was the same meeting that Koski was at. And I thought it was a very interesting proposal and I thought we were going to examine it more and consider this as an option because it is one of the ways of getting away from the conflicts of interest. It is also another way of dealing with multisite proposals, research trials. So I was just interested that we spent quite a bit of time listening to people, never discussed it, and I could not really find it. It certainly was not in the recommendations. So I wondered if it was something worthwhile bringing back into play or is it

too late.

DR. SHAPIRO: It is just my own judgment, and it is probably colored by other considerations that you have not mentioned, that that is not at least in the horizons we have workable myself. I think that --

PROFESSOR BACKLAR: Or feasible.

DR. SHAPIRO: Yes, I mean it is feasible in principle because you send the paper somewhere else instead of over here. It is very simple. I do not think it will be feasible for us. And I think there is issues that we have not discussed here and probably are not up to us to discuss regarding the liability, the legal liabilities institutions face in this area, which I think mitigates against this when they really get down to it even though I know some institutions are using independent IRBs now. We will see what happens over time. That is just my own judgment. It does not have to work that way.

Steve and Larry?

MR. HOLTZMAN: Well, I think how I got comfortable with it is the move we made here suggesting that at least half of the committee be not affiliated with the institution. That is pretty close and we have got people whose -- I thought that worked pretty well.

DR. SHAPIRO: Marjorie?

DR. SPEERS: Just to point out that in a

sense recommendations 4.8 and 4.9 to some degree deal with the issue that you are raising about using or being able to use IRBs that are outside of the institution. We -- in these recommendations in a way we changed them and one of the significant ways we changed them was to say that we are probably not ready to recommend another system outside of the local IRB system but we could move towards that particularly in review of multisite studies.

So in a sense -- I mean, I think that those two recommendations, coupled with recommendation 4.11 that deals with the number of members, the percent of members that are not affiliated with the institution address the independence of the IRB potentially.

DR. SHAPIRO: Steve and Larry?

Well, Larry, why don't you go first.

Steve, are you still on my list here?

Larry? And then Bernie.

DR. MIIKE: So where are we on conflict of interest? I am asking that in the sense that --

MR. HOLTZMAN: We are "agin" it.

(Laughter.)

DR. MIIKE: No, because -- what I understood Bernie to say, and my concerns about some of the institutional conflict of interest issues is that, are we or are we not even going to suggest that there are certain circumstances which we probably will not be able to specify in which it should be prohibited?

You know, we have talked about equity interest, et cetera. So -- and you know that happens in institutions, too, but that is a big step to say that a medical center cannot go into partnership with Millennium Pharmaceutical dealing with patients within their own medical center. But those are the kinds of conflicts, I think, that are pretty obvious about what is to -- you know, not just the potential there but it is a natural conflict from my standpoint. So are we going to just not address that specifically or what?

DR. SHAPIRO: My own sense of it now, Larry, is that we really need to do more than we have here in, identifying the nature of some of the conflicts and separating out the institutional conflicts and the individual conflicts. I, myself, do not feel prepared even in the individual case to articulate prohibited cases even though I recognize there are some.

DR. MIIKE: No, I understand that. I know we cannot do that but where are we going to come down? Are we going to say that there should be circumstances in which such arrangements are prohibited or are we just not going to say that? And just leave it open.

DR. SHAPIRO: I am not really -- I do not know about it. I do not have a view on that right now.

Bill?

MR. OLDAKER: My feeling is --

DR. SHAPIRO: I am sorry. Excuse me. I am sorry. Bill, go ahead.

MR. OLDAKER: My feeling is that if we make a recommendation -- it is very hard to figure out what should be prohibited in various settings but I think that if we figured out how to let the sun shine in and have disclosure, not only to basically the research subjects, but a public disclosure that is required on a universal basis that people could look across the board to see what those financial interests were. You know, to a certain extent that type of disclosure will have a way of forcing people to be introspective and regulate themselves.

So I think the first step of any type of conflict is if you can get the information out there and make it publicly available, and then I think a lot of other things flow from it. And that is not to say that it should not be given expressly to the research subjects also.

DR. MIIKE: Let me answer that by saying that there was an example given to us, I think, by Alta and I do not know whether the -- I cannot vouch for the facts being true, but my understanding was that there was an academic center in partnership with the pharmaceutical firm with patients getting in those institutions where there would be a biopsy

specimen and I think the words we used was they would take a little bit of extra tissue for research purposes.

If I were a patient and I am about ready to sign my consent form, what position am I in to say no? So I only use that as an example of asking a question about whether we are even going to make a general statement that there should be certain instances where such arrangements are such a conflict that they should be prohibited versus just sort of saying we are not going to say that and we are just going to say that really disclosure is what should take place.

So I am not asking for specific instances.

DR. SHAPIRO: I understand.

Bernie, and then back to Bill, and then I will give you my sense.

DR. LO: Two general points. First, I think disclosure works much better when you are disclosing a financial interest of the individual investigator pertaining to that trial you are entering. If it is disclosed to me, as a potential subject, that UCSF owns $2.9 billion of equity in various pharmaceutical and biotech companies, I do not know what to make of that. Whereas, it is a lot easier for me if I hear my doctor is being paid $50 to enroll me versus $10,000 to enroll me. That has some resonance.

My second point is really a question. I

mean, one of the difficulties I have thinking about institutional conflicts of interest is I do not have any analogies. So with individual conflicts of interests, I think, what do we do for government officials, what do we do for lawyers, things like that. Does anybody know of good examples of how institutional conflicts of interest, financial conflicts of interest are handled in other walks of life? I do not.

DR. SHAPIRO: Bill?

MR. OLDAKER: Actually I do but -- and maybe that is what I am drawing on here but the fact, as you said, that the institution is forced to disclose that it has X millions of shares or whatever it is of any corporation, I think you are right, it is not that helpful to the individual research participant.

But there are different levels of people who will scrutinize this information and so I think that, by forcing the information to be put on the public record and the issue that was put forward here, if there are different methods of paying, you know, that are coming in and those also had to be set forth on the public record and they are available to public scrutiny, many times self-regulation takes over and the university or the ethics officer at the university or of any organization is going to say do we really want to do it this way if we had to publicly disclose it.

In most of the -- you know, there are a number of various levels of ethical disclosures that have to be made by people in government and by people who contract with government. But the most effective part of that usually is the public exposure part of that. That causes kind of a self-regulatory apparatus to go on.

So -- and when you try to regulate it on a more close basis that you can own 25 shares but you cannot own 100 shares, you usually find the systems start to break down because no one can define where these lines actually should be drawn.

DR. SHAPIRO: Larry?

DR. MIIKE: The very disclosure forms that I signed for this Commission, I assumed that there is a ruling that says, oh, so you have a 100 shares of Merck, big deal, there is no conflict, you know.

(Laughter.)

DR. SHAPIRO: At the right time, I hope.

DR. MIIKE: But I assume that, within that system there can come a time where they say you are too much in conflict, you cannot participate in this particular area. So it is not just simply disclosure. It is disclosure for a purpose. It is not just to say, oh, we know that that person has a few stocks in that but it is also disclosure to the sense that this is too much of a conflict and one must recuse themselves from a particular decision.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: I would suggest that the staff take a little bit of a historical perspective here and look at the literature as it has developed over the last 20 years because, when research institutions, universities began to get into these equity situations with their professors in the biological sciences, molecular biology and so forth 25 years ago, there was a lot of concern within the universities, and it was not aimed at that point, towards the human subjects research aspect because we were talking about science that was not at that stage yet.

But in terms of the distortion of the research agenda, the effects on laboratories, the effects on graduate students and post-docs, what research they would work on and how much their research would come under proprietary headings and so forth, there were a lot of concerns.

And the extent to which this has now grown up and become much more customary, as people like David Blumenthal had written a good deal about, there has been, I think, a little bit of an ethical coarsening, as it were, or something. I mean, we have become inured to certain kinds of arrangements that would have amazed research administrators or presidents of organizations and chairs of departments 20 years ago.

And I have the sense that we may be sliding into the same thing now that we're in the human subjects arena and the notion that individual subjects should be put on the spot of deciding that they cannot -- thank you, Eric -- that they cannot -- I always like accompaniment to my perorations, -- that they cannot trust the institution because the institution has an equity arrangement with this or that biotech company whose product is about to be tested.

I think that does put it out -- yes, there is value, and if it is a patient with a disease for which there is an active patient organization that will take this up and say, well, the institution should not be involved in that way, or there should be some protections, that is fine. But individuals are not going to be in a good situation to do that and that really kind of undermines the trust that they ought to have in the institutions where they are having their research.

But I find it as unacceptable to think that an institution is involved in that way as I would again, to take the crass example, as if the institution were told we will test this and I will donate a million dollars if you come up with good test results that allows my product to be approved.

And yet that equity interest is, in effect, that gift of a million dollars. You go from a small

investment basically to suddenly having a stock that is worth a lot of -- a million might be a modest description of what could happen to the endowment with some of these entrepreneurial arrangements.

And there are all sorts of ways in which the choice to engage in that area of research rather than saying that research is a little premature, we should not be there yet, but the choice of what resources to put into it, what subjects, what patients are going to be allowed to be recruited, how the work is going to be supervised, and so forth, you can set up a whole institutional frame of mind that seems to me disclosure is not enough to prevent harm from arising because of the biases that that financial aspect introduces.

And I think, if we were having this discussion 20 years ago and we had respected physicians and researchers around this table, as you all are, they would say, no, we could not possibly do that. There has just been a change in mind set and it may be that the change is appropriate, Mr. Chairman, but it may be that we ought to step back and look at it through the lenses of time when this was not part of the landscape and say it is also possible that we have gone further than we really should have. And whatever is true of basic research, we have additional risks that are introduced to the process when human subjects are involved, and the

institution as protector of those, which is what the whole framework of the IRB is, the institution is protector of subjects, is undermined by that conflict. And we are going to have to endow universities and medical schools through other methods than allowing them to become so financially entangled with the success of research projects.

DR. SHAPIRO: Bill?

MR. OLDAKER: Alex, I agree with you at base. I guess what I am looking for is a practical and do-able solution. The universities out there know of this conflict at the current time and in my reading, and I could be wrong, there is only one university that is taking any proactive stance on this type of ownership.

And -- but there is no adequate disclosure the people could look at that would cause a ground swell of people to look at it. So what I am suggesting is a practical solution that will cause basically the population to be able to know what is going on and then you may get the change that you are talking about. I think it is rather difficult to get there in one step. That is all I am suggesting. I would agree if we could get there -- get back to where we were 20 years ago. I would think that would be the best possible place to be.

PROFESSOR CAPRON: I was not saying that I thought we should have a recommendation that

prohibits it. I thought we should have a discussion of it and point out the difficulties and your suggested solution may be the appropriate step-wise way of reaching a re-examination of the practice.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I agree with you, Alex. I think we need the discussion but I am not sure that I would say that it is a coarsening; although it is a changed world because I think there were equally insidious forces at work 20 years ago that just did not have names like stock options. All right. And if I look at who are the major endowers of those medical research institutions that hold stock as high fliers, all right, they still get a heck of a lot more money from big pharmaceutical companies not in the form of options or stock. And if the premise is that money will corrupt, money will corrupt whether it is in the form of a check or in the form of a trade-able security.

PROFESSOR CAPRON: It is the linkage.

MR. HOLTZMAN: Well, see that is the point about the insidious nature of linkages. What you have got in one -- you know, there is a view of the world in which it is so blatant when it is a stock option that the disclosure really is very, very powerful. When it is more indirect, and who knows whom, and who went to school with whom, and who is going to walk down the hall and say push this trial

along, and we are going to get this, those things exist, too, right. And so I mean it was much more gentlemanly with everything that is wrong with the gentlemanly world so to speak.

DR. SHAPIRO: Well, in the world that we actually have now in which we are going to issue some recommendations, it seems to me that when there are these -- talking about financial conflicts of interest. When there are these financial conflicts, which one way or another compromise an institution's integrity and that is a serious matter. Institutions worry about this all the time, whether it distorts the scientific agenda, whether it distorts research, I mean there are all kinds -- I do not want to go through a long litany here. And to get to Larry's question before, if you are asking the question can I imagine or should we imagine -- should we even say that sometimes these conflicts can become acute enough that you ought not to be doing that, I think -- or some saying like that --

MR. HOLTZMAN: Yes.

DR. SHAPIRO: -- I think that is entirely appropriate if that is the answer to your question.

But I do not know how to quite articulate it. As you said yourself, I mean you did not ask for that. But I think it can be serious enough.

Now these conflicts arise -- for universities these conflicts arise throughout the

research effort, but we, of course, are concerned with human subjects research, which is a subset of these in which these matters are more acute because of the risks directly taken on the shoulders of individuals and, therefore, we have an obligation to say something about this and to caution about it at the very least.

So we will try to do something just to strengthen and improve this discussion and recommendations on the basis of the kinds of things that have come up today.

We only have a few minutes left and Eric was anxious for us to look at the one recommendation we have in five. And so there are some things that will remain undone.

Eric, what did you want to point out about 5.1?

DISCUSSION: CHAPTER 5, "SUMMARY"; CHAPTER 1, "OVERVIEW"

DR. MESLIN: We just wanted to ensure that you had a chance to express your views on it.

DR. SHAPIRO: This is the one about resources, right?

DR. MESLIN: Exactly.

DR. MIIKE: There is no mention here about additional -- you are just exhorting the agencies and the industry to provide money for these areas. Could we be more specific, for example, we are asking

Congress to adequately fund this central office?

The issue here, of course, is that if there is within the budget additional monies to put in, in the research agenda for it, it will be a whole lot stronger. So whereas we should be asking that there be an addition to the research budget of -- we do not have to name a percentage but certainly -- so that it is not robbing Peter to pay Paul in terms of the indirect cost issue or monies that the agencies have for research because the money they put into this area where they would take on funding a research --

DR. SHAPIRO: Yes.

DR. MIIKE: -- so perhaps we should be doing something more --

DR. SHAPIRO: It is -- however, Larry, to use that -- it is robbing someone, right. You have got to rob someone to get this. This does not come free is the point. And those funds will have to come from somewhere, i.e. not go to somewhere. And I guess the point you are making is you would -- if I understood it, is that you want to protect the research allocation from having to contribute to this. Is that right? Okay.

DR. MIIKE: If we are talking about a zero sum -- zero incremental budget, then that obviously has to happen. But why not have -- because we are pushing for a whole system change, the whole system change costs money.

DR. SHAPIRO: Correct.

DR. MIIKE: It does not make sense. It does not make sense to say, oh, there is this radical change, by the way you go find money within your own agencies. It just does not make sense.

DR. SHAPIRO: Okay. I understand.

Bill, and Bette, and then Trish.

MR. OLDAKER: My fear -- I think this should be done, but my fear without greater specificity, if you either talk about the administrative overhead cost, all of this will get eaten up in various other ways. I would take the most effective way if we could figure out how to -- I do not know how to quite write it but -- or even how to say it possibly but we want some separate allocation of money that can only be used for the ethics and the ethics enforcement on these grants.

So -- and I am not sure what it is. If it is one -- I do not even know what the administrative overhead -- but, you know, say it is one percent or just one-half. Because otherwise, you know, in all of these everyone is trying to lay their hands on every dollar and unless you can somewhat sequester that money it is -- you know, it is going to get spent twice by other people to do other things.

So I think the only way it will be done is if someone could figure out how to write it in a way that we can have a certain amount that is put forward

for just this purpose.

DR. SHAPIRO: Bette?

MS. KRAMER: I would support what Bill said but I would extend it a little bit further and maybe you meant it to be inclusive of this, and that is that institutions should be required to -- and again I do not know how you stipulate what it should be, but to fund a staff for IRBs so that it does not become an add on to someone's function because otherwise there is no way it is going to be handled the way we are saying it ought to be handled.

And again I mean what keeps coming up is the amount of research that is being done other than at the major institutions where maybe it is attended to but not once you get away from that.

DR. SHAPIRO: I should point out in that regard that there are a number of initiatives ongoing now through other organizations, I think Marjorie may have mentioned that somewhere earlier on the document, which have made recommendations precisely of that kind and precisely dealing with those issues. And we may be able to just, in part, refer to those and support them in some way in the text or something.

But there are for different reasons -- for example, university presidents have all of a sudden been seized by this issue primarily because of the close of the actions obviously. They suddenly get

the light. They got the light because of the threats of obviously what behaving inappropriately meant. And so -- but nevertheless, for whatever the reasons, some of the recommendations go directly to this issue, that is how you compensate IRB members.

You know, Alex mentioned before that we ought to make the IRB members independent, which I quite agree with. On the other hand, if it is an assignment that nobody wants, this is sort of an empty protection, right. You want to only protect something that is worthwhile and so that these things interrelate with each other in that way.

PROFESSOR CAPRON: In my experience, everybody who is in a faculty positions and maybe some people in staff positions, have some institutional service obligations, and there are, in every institution I have ever been associated with, a subset of people for whom these are important issues and many of whom serve for many years very dedicatedly, very conscientiously, not in just a routinized fashion on their IRB. And, yes, like all assignments, we all groan if we are asked to do any particular assignment but someone for whom this is an activity that is worthwhile -- the outside people, I think, increasingly are compensated, not at any exorbitant rate, but some recognition that not only in the meetings but outside of the meetings there is a lot of work to do conscientiously.

If I could make just one question to staff.

DR. SHAPIRO: Could you wait, please? Because Trish has been waiting patiently?

PROFESSOR BACKLAR: I just -- this really directs me back to the conflicts of interest issues because what Alex said before about a coarsening of the ethics has actually in many ways come about because medical schools and these institutions have really become very impoverished, believe it or not, in the last few years. And the research is a way for them to survive.

And so here we are feeding one thing to another and we are talking about protecting the human subject but one of the issues is that medical schools themselves have become so needy that they need to press to do research with human subjects in order to make money to keep their hospitals and everything else going.

And I think we should at some point address this in the text somewhere because it is part of the real problem.

DR. SHAPIRO: That comes up at least in a small way in at least one sentence in chapter 1 but you are pointing out that is not adequate to what you have in mind but that is an issue, certainly an issue.

Alex?

PROFESSOR CAPRON: I just want to suggest

that staff might be able through either sources with long memories in Hill appropriations, staffs, or again the AAMC, or other -- the academic health care centers, to find out if there are examples of prior requirements. For example, in the radiation safety are, or other research, requirements which imposed additional burdens on institutions engaged in those activities and whether there were ever situations in which it was recognized that there should be funding available to allow those activities to be undertaken.

I do not go into that with knowing that there are such examples but it would be worthwhile knowing if someone can recall, yes, when we added on the requirement that you install level 3 labs to do this kind of research it was recognized that that was an additional cost and some money -- extra money was put into the budget to allow institutions to equip themselves that way because if there are such examples we should just have them and cite them.

DR. SHAPIRO: I think that is a good idea. I cannot cite examples in the biomedical area but there certainly are examples in other research areas where that is true. The Department of Energy, with respect to environment and so on, where additional monies were provided for clean up and things that -- new environmental requirements of various kinds and there may be very good examples in the biomedical area as well.

PROFESSOR CAPRON: So we could use others, the environmental area.

DR. SHAPIRO: Right. Okay. I think that it is -- Bette, I think -- I think we have probably gone on long enough and perhaps maybe too long today. It is already after 5:00 o'clock so I want to bring us to adjournment. I will spend a few minutes tomorrow morning before we get into the international research report, which we will devote most of the morning to, to just laying out what the next steps are here and how we expect to go from here to our next draft and so on. We will do that tomorrow morning.

We will go through 12:00 tomorrow. We will not go beyond 12:00. I do not know what Commissioners' schedules are but I know some will have to leave at that time, including myself. So we will -- at least I certainly will not go beyond 12:00. If there is a great demand to do so we will appoint someone else to chair in my place but thank you very much for your presence here today.

(Whereupon, at 5:10 p.m., the proceedings were concluded.)

* * * * *