44th MEETING

NATIONAL BIOETHICS ADVISORY COMMISSION

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I N D E X

P R O C E E D I N G S

PROFESSOR CHARO: All right. I recognize that there is little bit of difficulty with the electrical power over here but I think we probably should just get started and move slowly into the real meat of the day.

Good morning. And to those who are not members of the commission, welcome to the 44th meeting of the National Bioethics Advisory Commission.

We will be spending the two days entirely talking about the domestic system of protection of human participants in research. There will be an opportunity for public comment at 1:30 this afternoon. Those people who have not already indicated that they would like to speak are welcome still to sign up and there is a sign up sheet available for them outside of the room just as you entered and we ask that you keep your oral comments to five minutes but we welcome written submissions of any length and encourage people to participate. People should feel free to speak about any topic related to our work, not just the work that we are doing these two days.

I would like to turn the microphone over to Eric Meslin for some opening remarks and the executive director's report.

OPENING REMARKS

ERIC M. MESLIN, Ph.D.

DR. MESLIN: Thanks very much, Alta.

I just want to check. Rhetaugh, are you on the phone

with us at this point? No. Is Elisa or Deborah on the phone with us at this point?

DR. DEBRUIN: I am here, Eric. This is Deb.

DR. MESLIN: Hi, Deb.

DR. DEBRUIN: Hi, Eric.

DR. MESLIN: Just to let commissioners know that there are some absences. Professor Dumas will be joining us later on today.

I first wanted to, on behalf of the chair, Harold Shapiro, express his apologies for not being able to make this meeting today and his appreciation to Alta for chairing in his absence.

We distributed a number of materials to you electronically and in other forms, and although we do not spend a lot of time talking about either the legislative update that Ellen Gadbois prepares or the executive director's report, this is the only opportunity in the proceedings where you have a chance to discuss those.

And if you have questions of either Ellen or me about these items, please let us know.

I do, however, want to take an opportunity to flag just a couple of things for your own information. First, we are well underway with the public comment period of the International Report. For the public's benefit, who is here, that report, copies of which are outside, have been distributed widely both

throughout this country and around the world. We are getting comments in now. At last count there were probably 20 or 22 comments that had been received by various forms. The public comment period on that report closes on November the 13th.

I also want to point out again if you have not read the report that I have prepared that the commission has reserved the 22nd of November for the possibility of having a commission meeting via teleconference. We have not decided that that will occur but I wanted to let the public know and to confirm with commissioners that that was the date through our polling method that was best for all.

Once we get closer into the completion of the comment period we will have a better idea as to whether that meeting will be held, how long it will last and the like but I did want the public to be aware of that.

I am also pleased to tell the public as well as the commission that in addition to the reports we have been producing some other materials. The biennial report, the 1998-1999 biennial report, has been published. It is on our web site. Copies have been Fed Ex'd here to this location. They have not arrived for those who wish to get them. And it has a very comprehensive index of the commission's reports to date.

The only other thing I wanted to flag for everyone as a reminder is the time table for our oversight report. We have been optimistically planning with you, the commission, to produce a

public comment draft before the end of the calendar year. That is to say before the end of December. That essentially means that this meeting and the December 7th and 8th meetings will be when we will spend as much time as possible and any time in between to have gone over recommendations for that report with the aim of coming to some degree of closure on them and then going into a comment period in the beginning of the new calendar year.

We are aware that this is a very fast time table and, as you will hear from Marjorie, in a few minutes, it is one that we think is manageable but only with a lot of effort.

That is essentially all I wanted to brief you on. If you have questions about any of the other items in the report, including the global summit or any of the items in Ellen's very comprehensive legislative update, please feel free to address them to us.

PROFESSOR CHARO: At this point we are going to turn to Marjorie Speers for an update on the domestic oversight report and then we will begin with just kind of a brief introduction of how we will handle the discussion and materials for the rest of the day.

ETHICAL AND POLICY ISSUES IN THE OVERSIGHT OF HUMAN SUBJECTS RESEARCH UPDATE

MARJORIE A. SPEERS, Ph.D.

DR. SPEERS: Good morning. I think it has been -- it is probably fairly clear to all of you how the staff have been

spending their time since the September commission meeting. You have before you four chapters of the oversight report. We included Chapter 1 in your packets so that if you wanted to refer to the introductory chapter you were able to do so. But what we want to concentrate on today and tomorrow are Chapters 2, 3 and 4, which really are the substance of the oversight report.

We are planning to produce a Chapter 5 for you. That chapter will do two things. One is it will tie together everything that we have said in Chapters 2, 3 and 4. One of the points that we make in this report is that everything is interconnected and related to everything else and so we want to make that more explicit in Chapter 5 by pointing out some of those relationships and how the oversight system would work.

The second goal that we have for Chapter 5 is to relate this report to previous reports that you have produced and to show the relationship between those reports and this report. You do not have a draft of Chapter 5 because we wanted to wait until you have deliberated on Chapters 2, 3 and 4 so we know what needs to go into Chapter 5 but we will produce that chapter as quickly as possible and get it out to you via e-mail so that we can discuss it in December.

The chapters that you have before you are -- I would describe them as the core text for those chapters and what I mean by that is that it is our intention to add examples and text boxes with examples to those chapters. We will add those again after the deliberations today and tomorrow so that we know the

appropriate type of examples to add to those chapters.

We have also tried in these chapters to reference previous commission reports. We think we have done a reasonable job. We may not have done a complete job and so if you do find a place where something is missing, please let us know and we will make sure that we add that.

The same is true with the references. We do have more work to do on references in Chapter 4. There are no references in it because we just -- we were working on that chapter last week but we will be making that complete as well.

We believe that these chapters address all of the issues that we discussed in the outline for this report and in the work plan. So if you feel that something is missing please point that out but we have pretty much followed the outline and work plan and addressed those issues.

You have all of the recommendations for this report before you with the exception of one recommendation that I think will go into Chapter 5 and that will be a recommendation related to resources for this oversight system.

I think that that is all I want to say in my opening remarks and then I will make specific comments about chapters as Alta requests.

PROFESSOR CHARO: First, I have a feeling I probably speak for all of us when I say thank you very much. This has gone through a transformation in an incredibly fast -- with an incredibly fast turnaround time and it is impressive, and it is

coherent, and it is easily the basis for a real good discussion, and I just wanted to acknowledge that this was an extraordinarily good piece of work that we just got from the people who are working for this commission.

I wanted to just say a few things by way of preparatory remarks. The first is that although we do plan to go through recommendation by recommendation, Marjorie and I both feel that it might be helpful to give people an opportunity at the very beginning to make any over arching comments that they feel are not tied to a specific recommendation, whether it is things that you think have been omitted, things you think have been fundamentally organized in a way that is less helpful than another, et cetera.

And what we will do is we will take those comments and figure out when the best place -- where the best place is to talk about them. It might be right now this morning. It might be to wait and discuss them in the context of a particular chapter but we would like to give people a chance to make some comments that transcend specific recommendations and get that out on the table first.

And with regard to comments, in general, both Bernie and Trish were the first out of the box with comments on Chapters 2 and 3 and I suspect so quickly that some people had not even finished reading the chapters before the comments came through in e-mail so that their full value could not have been appreciated.

So at the point at which any of those comments are pertinent to the recommendation we are discussing, if I can invite

you both to repeat what you said on e-mail so that we all have it in our minds at a time when we can use it, it will make sure that they get the attention that they are due.

With that, let me ask if there are any kind of over arching comments or reactions having to do with things that are missing, misorganized, emphasized inappropriately, et cetera, and we will figure out how to handle them.

DR. CASSELL: It is not what is not there, it is what is there. I just -- I want to add my voice, Marjorie, to the others and say what a wonderful job this is. I mean, really, here is an attempt to rewrite the oversight of human participant research in the United States, which is daunting and the very idea of it is daunting, and yet I think that this is really very far -- a big step towards doing it right. I think it is wonderful.

PROFESSOR CHARO: Other comments before we kind of plunge into commas and periods and this word versus that word? Bernie?

DR. LO: I also want to thank Marjorie and the staff for really a tremendous job giving us a lot of material. I had four general comments. I made them on my e-mails but I wanted to sort of maybe just put them on the record in case the e-mails got crossed.

My first comment is that particularly Chapter 3 and Chapter 4, they are very theoretical and there were not examples to a reader who was not sort of really up on the in's and out's of human subjects research. There were not the kind of examples that

people would say, ah-ha, that is what they are talking about, that is where the problem is. And I think some of these could go in boxes or side bars but I think we need -- it is very dry and I think it is going to lose a lot of the public.

Secondly, I think it would really help if you had a summary of how what we are recommending differs from the current recommendations even just for us to look at as we work it through. And then I think we should go back once we see that and think about specific types of research that -- whose status changes, that would either be harder to do or easier to do, and just make sure we have it right.

Again, this goes back to -- my sense is this is a very theoretical sort of draft and I think we need to look at specific examples of controversial types of research and to make sure what we are recommending in general works out in specific cases.

A third comment is I think there is a general approach that we have developed and really are making here which may not be obvious to someone who has not been closely studying their reports. I think we are trying to walk a line between saying IRBs need a lot more guidance than is there under the current regulations and yet we want to give them some discretion.

In our other reports what we have done is said there should be a presumption that for this type of research da, da, da should happen but not always. There are these best practices that you ought to keep in mind and be ready to consider for this kind of research but we are not going to require you to do it in every

single situation.

I think that kind of flexibility is very useful particularly because we are sort of, as Eric said, redoing the whole house top to bottom. We want to make sure that what we are doing does not come out as so rigid that it ends up, you know, making the wrong decision in some cases.

And, finally, there are a lot of, sort of, special things in the current regs about children, prisoners and so on, and we do not deal with that and we may not want to, probably do not want to, but we should say something about whether we think it is okay the way it is or not because a lot of those are very much ad hoc kind of constructions for certain classes and it is not clear that the add up to a coherent policy but those, I think, are general comments that I think would help make the report as a whole more effective.

PROFESSOR CHARO: And, Bernie, on that last point on the special provisions, perhaps we can make sure to come back to that when we get to the section in the chapter that discusses vulnerable populations and notions of vulnerability and how one characterizes those moments and the rules that you follow. So let me invite you to bring that up again at that point. That seems somewhat tied to something we will eventually get to.

Other comments? Bernie's outline has a lot to do with -- at least in the first two areas with the writing of the report and the way in which it justifies the recommendations. We are going to focusing today only on the recommendations and not on the

text except to the extent the text makes an argument that is, you know, inappropriate but certainly comments -- over arching comments about the text or specific suggestions that are handed into the staff would be very welcome.

Anything else before we -- yes, Trish?

PROFESSOR BACKLAR: I also, as I said to Marjorie quietly as I came into the room, I also want to say I think this is a tour de force. Quite extraordinary, you, Marjorie, and your staff, my staff. Just amazing. I really congratulate you and we are all in your debt.

My comments actually were only on Chapter 2. I did not get you comments on Chapter 3. I did not want you to make me seem quite as quick as that. And I agree with much of what Bernie said, has already said. There was one thing I do not think that you brought up that I think was very important. My comments were much more things within the text and we can talk about that afterwards but I think this issue of direct therapeutic benefit is of some considerable concern and that is not simply something that is in the text that we can talk about and add and change around.

I think that is a conceptual issue that we have to speak about today because some of us feel very concerned. I am bringing this up because I am very concerned about it and we had the similar concern when we wrote the capacity report.

PROFESSOR CHARO: There are specific recommendations having to do with the characterization of research component by component versus whole intervention and when we get to that

recommendation can I ask you to bring this up again to make sure that we do not miss it because your concerns are imbedded in that recommendation.

PROFESSOR BACKLAR: Right. But it filters through in many other places.

PROFESSOR CHARO: It absolutely does. It is just as a matter of trying to organize when we discuss those and make sure we get through all the material.

PROFESSOR BACKLAR: And one more thing. There are some issues there in minimal risk clustered around with how minimal risk is conceptualized here that I would want to make sure that we all agree -- we have always had trouble with this and we should really address this very, very carefully so that we are sure that we are all at the same table and that what we are saying is very clear.

PROFESSOR CHARO: Right. And again because that actually is going to be in one of the specific recommendations, we will make sure that we get to it exactly when we have to decide whether or not we want to continue with that terminology and what it means.

Okay. Any other comments about things that might not appear in a discussion of the specific recommendation? Otherwise we will move on.

DR. MIIKE: Can I ask just a question? Marjorie, as you are going to start going through the chapters, I would like you at least to preface it and say why we are going to discuss three

before two.

DR. SPEERS: We chose to go out of order because Chapter 3 in many ways to me seemed to be the chapter where as a commission we had discussed it less among ourselves than we had the other two chapters, particularly Chapter 2. By that, at the meeting in San Francisco that we had in June, we had discussed as a commission the recommendations for the most part that appear in Chapter 2 and so our thought -- we had a fairly good idea of where the commission was headed on those kinds of issues.

For Chapter 3 we felt less certain and so we thought in terms of having an appropriate amount of time for a discussion we should start with Chapter 3 because we thought that would generate the most discussion and then move on to Chapter 2 that might take less discussion.

We had Chapter 4 on the second day because we knew we would be giving that chapter to you on Friday and wanted to give you even tonight, if you needed that, to read that chapter in order to prepare for tomorrow.

DR. MIIKE: I did not make the San Francisco meeting and I actually had more problems with Chapter 2 than Chapter 3.

PROFESSOR CHARO: We will absolutely get to it. In some ways Chapter 2, which focuses on the structural issues, is a vehicle for accomplishing the substantive things we want to accomplish in 3.

DR. MIIKE: With your recommendation, I have no problems with those few then.

PROFESSOR CHARO: Tom, you had a hand up?

DR. MURRAY: Excuse me. I will join in the chorus just to say thanks, Marjorie, to you and everybody else who participated in this.

We are asking a lot of the central office. We are making quite a few recommendations to them in Chapter 3, do this, do that, adopt these definitions, issue rules, et cetera. The good news is, of course, it is a new world of human subjects protections with a new Office of Human Research Protections and I suspect they will be more open. We have a historically open door and great opportunity to do this but also we are dumping an awful lot on them and just -- for our own deliberations we should maybe think about whether we see this as a package or a related package or whether we might want to communicate formally or informally a set of priorities. I mean if you have got -- we have given you 11 things to do, what are the three most important. Just to bear in mind as we go through the recommendations.

DISCUSSION: CHAPTER 3

PROFESSOR CHARO: That is a good suggestion.

Okay. At this point, with Larry's kind tolerance, we will move to Recommendation 3.1 and just slowly move through them since these really -- as I said, they represent the kind of substantive goals that this miracle office is supposed to achieve.

Recommendation 3.1: The central office should issue regulations requiring IRBs to consider risks, not only to research

participants, but to their communities who may be affected by the research. You will notice on the handout, by the way, that the staff has very kindly given you a page number reference of the text so it will help you remember the discussion that preceded that recommendation.

Comments on 3.1?

Eric? Eric, actually let me just say people should have found at their seats here a short collection of recommendations with no text at all which will help us focus on recs and avoid the temptation to deal with the commas and semi-colons in the text, but the page numbers of the text are there for illumination.

Eric?

DR. CASSELL: Well, my only problem with it is why single out communities and not families. It is really others who are directly affected by the research. I mean, there is always an indirect effect to them, everything one does, but I do not think we should single out communities. One general comment, in the attempt to be so specific and that we are totally understood, it begins to introduce complexity. But this is one of those places where we ought to be -- we want to just say "or others directly affected."

PROFESSOR CHARO: Do others agree?

DR. MIIKE: I guess this gets more into the question of how are these -- two things. One is how are these recommendations organized and the extent to which are some fairly global and others are very specific. So that if you read -- for example, in

this place if you read the text, I can see how Recommendation 3.2 comes out of it but I really do not see how 3.1 comes out of it and I guess that is sort of echoing what Eric is saying. I was actually surprised to see this as a very specific recommendation. It is the kind of thing that we have said before in our reports that in certain research projects that the investigators, the research protocol, et cetera, and of course by inference the IRB should be focusing on. So I am not sure whether this one rises to the level of a recommendation and I have particular problems with Chapter 4 on that issue. There are others in these recommendations where I think more commentary rather than the specific recommendation because I do not think we have to tell IRBs everything, absolutely everything that the IRB should be doing. I think there is another one later on that directs itself to -- I guess it is in the text where it says in our previous reports we directed this to investigators and then we come out with a recommendation directing it to IRBs, and it seems to me redundant. I mean, if investigators are directed to look at certain things then IRBs of necessity will be reviewing it and we do not need to reiterate that again in the recommendations.

So a long winded answer is while I find this chapter pretty good, I still think we need to go back, and this is not the time obviously to do it, is to see how these are organized and then see what -- whether some of these kinds of things would drop out of this and remain back in the text.

PROFESSOR CHARO: Just as an aside by way of

information, one of the things that the staff had talked about doing is taking today's discussions and changes in the recommendations that we agreed to today and trying to rapidly assemble them and redistribute them so that people can then see from kind of global -- in a global fashion where we have come out and that may be a good opportunity at that point, Larry, for you to revisit whether or not you think these are inappropriate.

DR. MIIKE: I do not want to get lost because we are addressing these recommendation by recommendation. I think on the whole they are really good. It is just that we have to tweak the presentation and whether some of these should really drop out specifically.

PROFESSOR CHARO: Bill?

MR. OLDAKER: To join the chorus here, I saw Marjorie last night, I think this is an exceptionally good job and I also would echo that I think some -- I think the product is all there and I think some reorganization as we go through will probably be helpful but I do not think that will be that difficult because I think Marjorie has done a great job of pulling these together.

Let me echo what Eric says, at least about the first Recommendation 3. I think that we should make sure that we narrow the coverage here so that we are not covering more than necessary. If we want to have strong enforcement, I think we have to make sure that the breadth of what we are talking about is specific enough that people will take it seriously and so I would use directly affected by the research so that we can actually tell,

and people will specifically understand, what they are dealing with here. I think the language as it stands is so broad that most people may not understand exactly what their responsibilities are.

The second thing is much more minor, although I think in the final analysis we have to worry about public perception of our report. I think the term "central office" has an air to it that, you know, probably is not the best. I would suggest that we come up with a term like the Office of Bioethics or something that we insert in there just as a filler term, whatever it is, and just not leave that there.

PROFESSOR CHARO: Reminiscent of the Politburo, is that the --

MR. OLDAKER: Yes.

(Laughter.)

PROFESSOR CHARO: Diane?

DR. SCOTT-JONES: I just had a question about -- are we still looking at Recommendation 3.1 --about risk to the communities? I know you do not want us to focus just on the text but I am just -- I am looking back to try to find the supporting text and is it on page 7 because it does actually talk about other than communities. It talks about families and it is much broader than the Recommendation 3.1, but I believe that is really the part of the text where that comes from, isn't it?

PROFESSOR CHARO: Mm-hum.

DR. SCOTT-JONES: There is nothing on -- page 16 is

where this appears but it is not where the supporting text appears so it is really already there in the text.

DR. SPEERS: The text is on page 7. It starts at the bottom of page 7.

PROFESSOR CHARO: Arturo?

DR. BRITO: I, too, found this recommendation -- you know, there is a slight bit of a supporting text here somewhat out of place, but I think it is an important recommendation to consider others other than just a research participant, and one of the thoughts I had was -- and this goes along with what Bernie was saying earlier about making it not so theoretical, but maybe here is an opportunity to provide a specific example with all the genetics study potential there is in the future, I think this is where a lot of these -- the need arises.

So maybe with the supporting text in there maybe providing an example of that, and I am not sure this is the place for it and I am not sure it is so important, but I do think this recommendation is important because I think this is going to become even more so important in the future.

PROFESSOR CHARO: I think for those commissioners who had some experience working on IRBs or doing research in the field this would be a great opportunity to share stories that would illuminate specific recommendations or concerns in the text and we can certainly write a series of little narrative boxes that answer Bernie's concern.

DR. BRITO: And one little fine point, but maybe not use

the word "communities" here as somebody said earlier but to research participants and those that may -- you know, some language of that nature, but that is easy to do later when we decide.

PROFESSOR CHARO: Other comments?

The way I have it redrafted based on the comments would be "The central office should issue regulations requiring IRBs to consider risks not only to research participants but to others who may be directly affected by the research." Is that something people can agree with?

DR. MURRAY: I think it is a good crack at it. We may want to refine it.

PROFESSOR CHARO: We will see -- when we see tomorrow, we will see everything else comes out, if that is acceptable. Okay.

Recommendation 3.2. Let me just ask do members of the audience actually have copies of these recommendations? Okay. Well, then there is no need to be reading them out loud.

Let me direct your attention to 3.2 and ask for comments.

Larry?

DR. MIIKE: The term -- what is it -- "research equipoise" is a little obtuse if we are talking about people understanding what it means. I had to go to the chart to see exactly what we meant by that. So just a suggestion that we find some more common words than that.

I think this is also an example of the arrangements of these research -- these recommendations. It seems to me that one and two are really the ones that we should be starting off with, and if we are going to keep one, that is really to me misplaced at the moment.

PROFESSOR CHARO: Okay. So we may have to go back to the organization of the order in which that appeared.

Bernie?

DR. LO: I have a number of concerns about the treatment of risk and how we categorize risk. First, I think there are two separate issues that get confounded here. One is the issue of do you look at the risk of the protocol as a whole or component by component? And the second has to do with this really difficult question that used to be called therapeutic versus nontherapeutic. Previously in previous reports we called it prospective of direct benefit versus no prospect of direct benefit. Now we are introducing a new term of research that intends -- component designed to offer a direct benefit.

I think this is similar to what Trish was driving at. I am just very concerned that research is not therapeutic. Research is not intended to provide a benefit. Research is intended to ask a question as to whether an intervention provides a benefit or not.

So I think this whole language, that you can design research whose intention is to provide direct benefit to the patient as opposed to asking a subject to enroll in a trial that

is going to answer the question of does it work, I think really needs to be worked through. So I think this whole notion that underlies the text around 3.2 and to some extent the table, I just have a lot of trouble with.

PROFESSOR CHARO: Diane?

DR. SCOTT-JONES: I have a question about the role of the social, behavioral and economic sciences in this because if you look at the Figure 1 the way it is set up, it pretty much would not apply. Although I know that Marjorie has done a wonderful job of being attentive to the social and behavioral sciences, but, you know, it refers to the committee of expert practitioners and the preferred intervention and those would not apply to all of biomedical research because there would not always be an intervention in mind at the time that research is conducted, but it completely gets away from the social and behavioral sciences if you are using this model as the way that all research should be reviewed.

PROFESSOR CHARO: Eric?

DR. CASSELL: Well, I am also troubled by the question. It is -- I think what you are talking about is that those things that have -- that are designed to test therapeutic interventions versus those that are designed to produce new knowledge not directly related to therapeutic -- because when you say benefits you get into -- it is an oxymoron in the way it is written at the moment.

But I take it that is what you mean. Those are the

things that -- where a new therapy is being tested. Is that what you mean?

DR. SPEERS: Yes. If I could clarify.

PROFESSOR CHARO: Please, Marjorie.

DR. SPEERS: If I could clarify, that is right. It -- as I am listening to this discussion I am thinking that this may be a semantic problem. It may be more than a semantic problem, but at least at the minimum it is --

PROFESSOR CHARO: So is the Declaration of Independence but, you know, we have to be careful.

DR. SPEERS: You are right. What you say is correct and could I also --

PROFESSOR CHARO: Please.

DR. SPEERS: -- clarify -- I want to talk about the socio-behavioral sciences as well and what we are trying to do here. We were trying to come up with a model that could be used to analyze risk and potential benefit for all types of research, and we were recognizing that virtually everyone thinks about clinical research, and so trying to think about terminology that we could use that would apply to other types of research, and that is why, for example, we try subtle things. Instead of using the word "treatment" perhaps to use the word "intervention", because in clinical research we talk about treatments. In public health research we would talk about interventions. In psychology or economics research we talk about interventions. There are interventions, and we may have missed the mark but that is part of

what we were trying to do.

The same with the term "research equipoise." I was concerned if we used the term "clinical equipoise" then one would think it only applies to practice in medicine and not practice in other fields.

PROFESSOR CHARO: Larry?

DR. MIIKE: Well, my problem is not with the word "research." My problem is with the word "equipoise." Okay. But in answer to Diane, let me just sort of support what Marjorie is saying. I think what her model envisions -- is sort of an algorithm that one can try to apply to any kind of research. So in the terms of what you are discussing we are just simply going down the right arm of the protocol because there are no other expected benefits. So I think that the model does -- can be applied to the clinical research that you talk about.

I am looking at the sheet way towards the back that summarizes the protocol that one goes through.

PROFESSOR CHARO: Tom?

DR. MURRAY: But, of course, in socio-behavioral research you might think of some benefits. It would not be medical benefits but suppose you were trying to get some theories about how children learn to read, and you wanted to get both some knowledge about how developmental reading takes place but you also wanted to try some new methods of encouraging children, say, who had certain problems with reading so that would be -- that would go down both sides. It would go down the right-hand side and it

would go down the research questions on the left-hand side. It would be whether what you are exposing them to is, in fact, at least, you know, arguably in equipoise with the standard teaching.

DR. MIIKE: No, I agree and I guess what you are trying to do, Marjorie, is to say that IRBs when they review these should more or less have a checklist that it can make sure that they are reviewing it in total rather than in a haphazard way. Just sort of providing guidance to them.

PROFESSOR CHARO: Arturo?

DR. BRITO: I like this -- you know, I read this. I think it was a very good model and -- semantics aside and I think those need to be tweaked out and I think it is a very good model. And I think the way I was thinking is this left side -- you know, offer benefits -- was really what, in my mind, directly could impact, whether it is benefit or risk, on the participants. So if you are doing this research model on reading affects children, you are doing a global research question, which is, you know, how really effective is it with the children, or what have you, and that is on the right side.

On the left side is if you are enrolling an individual -- it is almost like you are taking -- back to this Recommendation 3.1 -- you are taking the individual on the left side and really society as a whole or a group as a whole or the community as a whole goes on the right side. But I particularly like it, but I do agree it is a little bit confusing if the word "benefit" is on the left hand side, but I thought it was clear.

PROFESSOR CHARO: Well, can I direct our --

DR. LO: I -- just frankly I am trying to understand this, so help me with a specific example. Walk me through this chart. Take whatever clinical trial, okay, testing a new drug. It seems to me the research question is does this drug work better than the control group, which presumably is standard of care. Is every -- what is in the left arm? What is in the right arm here? Is the fact that they are coming in and seeing a doctor every six months who may be a little more conscientious or detailed than the standard and what they are getting in the community, is that a direct benefit? Because it is not really designed to -- I mean, I am just really -- I am not sure how I separate the left hand column from the right. And then in both columns it seems to me there is a -- there are design issues as well as risk/ benefit issues.

PROFESSOR CHARO: Bernie, if I may take the privilege of answering that. The kind of biomedical model I had in mind, looking at this, was one of the many cancer protocols I have seen on our IRB where you might have, for example, a standard chemotherapy approach to a particular cancer and the research question is whether or not an adjuvant therapy that is added on after the chemo is completed would have any effect on long-term outcomes.

So that there would be people going through what they would go through even if they were not in a research protocol and then they have an add on that is specifically research oriented

but the entire treatment standard and research intervention is being supervised by the same people because they are trying to integrate with these particular individuals the interaction with the medical system.

DR. MURRAY: Alta, may I try?

DR. LO: I am sorry. What is left and what is right? What is in the left column and what is in the right column?

PROFESSOR CHARO: I do not have the chart in front of me. I do not know which one is left and which one is right. Left column would be the ordinary chemo that they would have gotten even if they had not been research participants and the components designed to answer the research question would be the add on, some randomized to having no add on and some randomized to having the investigational add on.

DR. LO: Okay. So the left column is just what they would be getting in the school in trying to understand how people read and it is just sort of standard care. Then why is research equipoise an issue that --

PROFESSOR CHARO: Have I misunderstood the chart? I have.

DR. SPEERS: Yes.

PROFESSOR CHARO: Okay. Sorry, Marjorie.

DR. MURRAY: Let me try a prosaic example. At a place I used to work years ago there was a physician who was a leading investigator of inner -- the treatment of inner ear infections in children. Let's just assume that he is going to try a new -- he

has got a new antibiotic he wants to try for inner ear infections. Let's see how we can understand that.

The research equipoise question, I take it, would be if there is reason to -- that it is reasonable to believe that the new antibiotic is, you know, at least as effective as the old one, but, of course, we do not know for sure so that would be -- that would satisfy research equipoise. So that is down the left hand column. I am just trying to state my understanding.

The right hand column would be the components designed for the research. Now what is different in the way we treat these children and what we do with these children? So maybe -- you know, I am not here, I am really out of my depth but let's say that we do various blood tests that we would not have done or that we have more visits to the doctor's office or to the researcher's office that otherwise would not have occurred. But all of those have to do with the evaluation of the research. They would all be down the right hand column.

Is that --

DR. CASSELL: That sounds to me like dividing it up exactly right. You could do the same trial by just doing different antibiotics. You would be there, and using only one endpoint and six month endpoints which introduce risk to the participants that has not to do solely with the question of is this a better treatment or not. So that would put it on both sides of that.

And then in that case virtually any trial of any

intervention can be divided up that way. Even the reading trial, how are you going to find out whether these children are reading better?

DR. MURRAY: The reading trial I thought had both right and left hand markers.

DR. CASSELL: Right. But you could do --

DR. MURRAY: There may be some trials with no left hand markers.

DR. CASSELL: Well, then you have to make that clear. I mean that has to be made as an example.

PROFESSOR CHARO: Bernie?

DR. LO: Well, first, I think we are having trouble here just sort of working it out.

PROFESSOR CHARO: No, actually I was the only one who had trouble.

DR. LO: It seems to me the test of -- this box on the left must pass the test of research equipoise, I always thought that was the stage one question. If it does not pass the test of research, you throw it out and do not do it. You either say it is just standard care or you say there is no justification for doing this because there is no research questions worth asking. So I am not sure why that question is not the first thing once you get the protocol.

Is there a meaningful research question that needs to be addressed and is the state of the art ripe for this type of study as opposed to some other design? So you have to answer that

before you start saying now let's see if the components -- to see whether the risks and benefits are appropriate and the risks are minimized.

PROFESSOR CHARO: Marjorie, did you want to clarify anything at this point?

DR. SPEERS: Again, what I think the value is in having it laid out like this is trying to come up with one figure, if you will, to deal with all types of research and so I think that that is one value of it.

The other is if we talk about IRBs today in terms of those that are skilled and those that are more skilled, the more skilled IRB might make that kind of an analysis but there are a number of IRBs that have difficulty in performing the risk analysis and do not necessarily break -- you know, they do not necessarily look at the various procedures in a protocol and have a sense of how to analyze the risk associated with the various procedures.

Part of what this model is doing is it is giving the basis for the analysis for the two different types of components. Whereas in the one it is saying that the basis is equipoise and in the other it is making a comparison between the potential risk and the potential benefit and knowledge.

And what it does is it -- and what we say in the text is that those procedures that may be intended to provide a benefit should not be used to justify the nontherapeutic procedures.

DR. CASSELL: In other words, you cannot be exposed to a

lot of risk just because their equipoise condition has been met?

DR. SPEERS: Right.

DR. CASSELL: They are separate issues.

PROFESSOR CHARO: Bernie?

DR. LO: Yes. You guys have got to help me because I am really having trouble with this, but it seems to me on the left hand column stuff that you would get if you are just an ordinary patient with ear infection or a little kid trying to learn to read has also to do with the quality of care. Does it meet the standard of care? So if the teacher is rotten and there is violence in the classroom, it seems to me it is unethical to do the study because you are subjecting the kids to risk.

So the risk surely should enter in the left hand side as well just as in the clinical trial if I am doing -- if what -- if the standard care I am giving does not meet standard care. I have not informed them that there is lumpectomy and there is other kinds of adjuvant therapy and I do not have a decent radiotherapist on the staff.

So it seems to me it is not just a matter of is there research equipoise, you are also saying does that component, what you are saying they would get anyway just by virtue of being a patient or a student, whether or not they are in the research protocol, aren't we asking the IRB to look at that with regard to risks and benefits? I think there is a risk and benefit component on that left side as well.

I think the point you were making originally, which was

you cannot justify risk just because you say, oh, there is some component of this study that has a prospect of perhaps providing therapeutic benefit, you cannot use that to override a whole lot of risk elsewhere in the study. That I support and I think is a good insight but I am not sure this table helps me to get to that insight. I just end up getting more confused when I look at the table.

PROFESSOR CHARO: Trish?

PROFESSOR BACKLAR: And I am concerned that when I look at this to begin with I see it feeding the therapeutic misconception and the people will look at this and say -- and, ah, well, you see there is a part of research that is really designed to benefit and that seems to become more powerful. The left side gets more power and the right side sort of recedes because then that will make it okay.

But I also actually really do agree about the equipoise and I think actually somewhere in the text you talk about -- you explain why you are using the word "research equipoise," which I think all of us -- or certainly I would agree with. But it is not right to put people into -- to take their time and I believe that you said that somewhere. I may have been thinking of something. It is not right to take people's time unless there is research equipoise. I mean that is -- I cannot see how you can start out without looking at that.

PROFESSOR CHARO: Tom?

DR. MURRAY: I appreciate the hard questions that Bernie

and Trish asked. I had taken this a little differently. I had taken this as an effort to solve maybe a different kind of problem. That is, where the benefits that come from the intervention are being used to justify the risks that are solely related to the research. I think that is a useful distinction. I did not -- I mean, I had no hand in this decision to do it this way, but I find it actually pretty illuminating because I suspect that that kind of slipping over probably happens a lot in the discussions about the ethics of research.

Do we have a new visitor?

PROFESSOR CHARO: Can I just ask -- can I poll the telephone participants and find out who is there with us?

DR. DEBRUIN: I am here. Deb DeBruin.

PROFESSOR CHARO: Hi, Deb. Anybody else?

DR. EISEMAN: Elisa Eiseman is on the line.

PROFESSOR CHARO: Hey, hi.

DR. EISEMAN: Hi.

PROFESSOR CHARO: And, Rhetaugh, are you on the line?

Okay. So we have got two of our three telephone participants.

Let me ask while I have got you there if you have got anything you wanted to add to our discussion.

(Simultaneous discussion.)

DR. MURRAY: But they would probably be shocked to know that three of the commissioners are stark naked but we are not going to --

(Laughter.)

PROFESSOR CHARO: Eric?

DR. CASSELL: I just -- I mean, I hear what is going on. I would like to just summarize it. So we have taken out the word "benefit" all together because that does not apply here. It has to do with therapeutic interventions that are designed to be therapeutic interventions. Benefit -- we do not know if they are going to have any benefit.

PROFESSOR CHARO: I am not sure what words are in or out but I --

DR. CASSELL: I am actually making a statement and a question. And then we have restricted the other side to the risks incurred in the course of the research. We are trying to divide up those two issues in this so that they are the risk incurred as judged solely on the basis of risk and therapeutic intervention is judged solely on the basis of equipoise. Is that what you are saying, Marjorie?

DR. SPEERS: What I am trying to say is for the nontherapeutic procedures that those risks are judged in relation to the potential knowledge that would be gained from the research. And I am saying that the risks and potential benefits for procedures that have the prospect of some benefit, so if I can just use the term "a therapeutic procedure," if I can slip into that. I am saying there that the basis for judging the risks and the potential benefits is equipoise but that is --

(Simultaneous discussion.)

DR. SPEERS: -- and then you can disagree.

PROFESSOR CHARO: Bette and then Bernie.

MS. KRAMER: Well, I am finding the discussion very confusing and I wonder how would that relate to -- or would this even be pertinent? Say a Phase I drug trial. I mean, this is designed to cover all kinds of research, correct?

DR. SPEERS: And I would say that --

MS. KRAMER: Every time I hear you use the word "therapeutic" I wonder, you know, something where there is by design clearly no therapeutic possibility.

DR. SPEERS: That is correct and so a Phase I trial would be judged on the right hand side --

MS. KRAMER: Solely.

DR. SPEERS: -- of a component only to answer the research question.

DR. MURRAY: I think it is a little more complicated than that. The Phase I trial done in a healthy normal adult, just to look at pharmacokinetics and things, clearly is just in the right hand side.

A Phase I trial done on a cancer intervention for an otherwise untreatable cancer is almost all on the right hand side. The FDA, the rules do say there might be some possibility, you know, it does not eliminate the possibility of benefit. It just says you cannot have any reasonable expectation of benefit so I am not sure how we would define that group.

PROFESSOR CHARO: Bernie, and then I am going to put

myself on the list.

DR. LO: If the left hand column is meant to be those parts of a research protocol to offer the prospect of potential therapeutic benefit -- potential direct benefit, it seems to me we need to look at the risks and benefits of those interventions, not just the equipoise, because I would just say -- you know, it is an open question. I can choose the most invasive, the most risky intervention to test without any attention to whether the risks are disproportionate to prospective benefits and whether the risks are minimized.

We have got the Common Rule so I do not think that is what we are trying to do.

DR. MURRAY: Bernie, I like what you just said. I think it is very helpful to me but it seems to me that is exactly how a definition or a judgment of equipoise is reached. It is a comparison of the risks, benefits, prospects of benefit of the two interventions, whether they are, in fact, in a rough balance. If that is true that is -- it may be constitutive of equipoise but maybe I do not understand either the concept of equipoise or --

DR. LO: Well, no, because there is a thing in the CFR saying you have got to minimize the risks even if they are in equipoise so that is not it at all. The risks have to be proportionate to the anticipated benefit so that they may be in equipoise and I would say this is just too risky to do. It is a fair question whether A is better than B but A is so risky. The prospect of doing, you know, xeno transplantation is an open

question whether xeno transplantation is better than heterograft transplantation. I may just feel the risks are too great.

PROFESSOR CHARO: Diane and then Eric?

DR. SCOTT-JONES: I am still thinking about how the social and behavioral sciences fit in here and I read back on chapter -- on page 13 where we have written that the social sciences basically would fit the right side and not the left side and I think Tom has already given an example of research on reading that does -- that would fit this model. You could, in fact, do a reading intervention or many, many other kinds of interventions so the social sciences could fit this same sort of model where there is an intervention that is being studied and tested.

But there is another question about exactly what research equipoise means and I understood it to mean before seeing this what Bernie said earlier, and that is that is what you do when you are deciding whether the research should be done in the first place. Is there sufficient uncertainty so that you do have a research question because if everybody knows that a phonological approach is better in reading then you do not genuinely have a research question. You would never test some other way against it because it is already known.

You would have to have some justification for doing the study in the first place so it seems that research equipoise as -- it is not exactly research equipoise that is meant here. It is something else because that is the first question before you

embark on the study.

PROFESSOR CHARO: Eric?

DR. CASSELL: Well -- excuse me. My understanding of equipoise is exactly the same. Equipoise to me means you cannot tell which is a better intervention, period. The question of risk is a separate question and we could give examples by the dozens in which something may be better but it is much more risky and so forth so that would have to be separated out. But from what I see here that does not threaten, that does not -- equipoise can be met and still risk/benefit is a separate -- risk is a separate part of the analysis.

PROFESSOR CHARO: Tom, is this directly in response because I --

DR. MURRAY: Yes.

PROFESSOR CHARO: -- okay. Then I will put myself on the list after you.

DR. MURRAY: I hope it is. Eric will be the judge.

I mean, at least as I have understood the concept of equipoise, let me give you a ridiculous hypothetical, the way I think usually. And that is two treatments for the same illness and sort of moderate -- causes moderate morbidity. And one of them, the side effects are, you know, a little rash that lasts for 24 hours. The other side effect is, you know, all of your fingers and toes falling off. But the probability of success of the two is identical. Both are equal -- both have a 75 percent likelihood of curing the disease.

Well, those are not in equipoise. The 75 percent likelihood of successful treatment is just one of the things that is the benefit piece. The risk piece is wholly disproportionate. So those treatments are by no means in equipoise.

So my view of the risk/benefit judgment about the intervention is built -- very much built in constitutive of the concept of equipoise. That is my understanding.

DR. CASSELL: Well, here we are. This is really important. I mean, first of all, it is such a definitional issue that it has got to be on the front cover of the report. Research equipoise is -- now you can define it any way you want to. My understanding was not that. You say, well, we do not know whether chloramphenicol is any better than tetracycline for middle ear infections and so they are in equipoise. On the other hand, chloramphenicol has a risk of fatal granular cyrtosis whereas tetracycline just makes your teeth yellow.

So we better clarify that, whatever we mean by that. If that is what research equipoise is, different from just ordinary sitting on a saddle evenly, then we better make that clear.

PROFESSOR CHARO: For sure, clarity will be the first priority.

DR. CASSELL: Well, in this instance, this is so important, it runs through the whole research enterprise.

PROFESSOR CHARO: Marjorie thinks that she may be able to help to focus our feedback by asking a question so let me turn to Marjorie.

DR. SPEERS: Just to pick up on what Bernie is saying and what I think I hear others saying, which is even on the left side an analysis still needs to be done of the risks and benefits.

My question to you is how should that analysis be done? You know, on the other side, I think we have agreed that the comparison is that what the IRB does is to make a judgment between the risks and the potential benefit of the knowledge gained from the research.

On the left side, how are the risks judged in relationship to the potential benefits? I think if we could answer that -- at least where I think the group is going, which is if we can clear up the language here, many of the ideas here are reasonable but this is a key piece that we are missing.

PROFESSOR CHARO: Eric, and then Larry?

DR. MESLIN: I just want to remind commissioners that the concept of equipoise is something we have been discussing for a number of reports and in the current draft of the International Report we spend some time carving out that territory.

We say, for example, that when used in the context of research, equipoise describes a state of genuine uncertainty about whether the experimental intervention or the control arm offers greater benefit of harm than does the control. In the clinical context, having reasons to believe that one intervention is superior to others ethically compels a clinician to recommend the intervention. However, in the research context individual

preferences are replaced by the collective uncertainty of the clinical community.

And the definition of clinical equipoise, which began with Benjie Friedman's 1987 article from which all of this flows, is the concept of clinical equipoise is that a trial is ethical if there is genuine uncertainty within the expert medical community, not necessarily on the part of the individual investigator, about the preferred treatment. Preferred treatment in this sense refers to both the expert community's assessment of whether the treatment overall, taking into account potential benefits and harms, is preferable to the other or new or experimental intervention.

So if that helps you, good. The idea just to remind you about research equipoise, and Larry was the one who said he did not have a problem with the word "research," his problem was with the word "equipoise," I think this may help you be consistent with what you have said in the previous report, namely that equipoise -- clinical equipoise or research equipoise, which is to cover the larger set of practices, is the collective uncertainty about two different interventions. Uncertainty on the part of a community of clinician investigators. And their uncertainty is related both to the overall benefit, potential benefit and risk.

DR. CASSELL: Benefit and risk, that is the essential.

PROFESSOR CHARO: Larry?

DR. MIIKE: Yes. I was -- well, two things. One was I was going to point people to the central paragraph on page 15, which discusses research equipoise in terms of risks also. And

maybe our confusion is that what we are really looking at in these two arms of the protocol is that what we are suggesting is IRBs should take two looks.

One is the risks and benefits that is applied to the individual participant in a situation where there are preferred therapeutic possibilities in the research. And then in other cases when there are not, such as the kinds of research that Diane gets into.

So I think what we are really doing is basically applying the same analysis to either arm. It is just that we are saying there is a heightened scrutiny when there is an offering of a potential benefit or therapeutic intervention or whatever you want to say. So it is not a distinctly different -- in these analyses down the two arms but the same analysis applies to different situations and maybe that is the confusion.

PROFESSOR CHARO: I would like to intervene now because, first, I agree completely, Larry. The significance is going to fall not in the way in which we analyze the risks and benefits. It is going to fall in the areas of things like surrogate decision making where we have created in other reports different rules for when third parties can make decisions for others depending upon whether or not something is absolutely certain to have no possible benefit to the research participant versus circumstances where there is that possibility.

But at the risk of making things even more confusing and knowing that we have got 13 recommendations to go through, I think

I have identified why it is that I was confused in the beginning, and it is because in some ways I think that the chart fails to capture a third -- so-called third arm here.

When I think about the protocols we have looked at, they have actually had three different components. Many of them have a component that is absolutely therapeutic. It is the standard therapy. It is the eye exam. It is taking the blood pressure or it is going through the ordinary chemo regime.

And a second arm is something that I am going to call "possibly therapeutic." And that would be where you are testing things on people who might possibly benefit from them but you are testing them because you do not know who benefits best from various kinds of interventions.

And then the last component is the one where there is no possible benefit or the truly nontherapeutic one. And when you add that third arm I think you capture where it is that I got confused to begin with but it is pertinent because we have had debates on our IRBs about whether or not it was appropriate overall to say that risks were outweighed by benefits when there have been enough standard therapy components that were made available to people who could not ordinarily have gotten them and that from the individual's point of view it was not a bad deal.

I think the classic kind of person that would fall in that category would be somebody without health insurance who does not ordinarily get good preventive care and suddenly they would get a whole panoply of preventive care interventions on the

condition that they also participated in another arm that was either possibly therapeutic or absolutely certain not to be therapeutic. Either one of which had some serious risks.

I am wondering if we can add that in, in the way in which we break this stuff out.

Bernie?

DR. LO: I thought what was very insightful about this part of the chapter was this notion that certain types of benefits are used to justify certain types of risks in a protocol and it is the risks that have to do with the interventions that have no prospect of benefitting the patient. We are saying you cannot justify those by the fact that you are either giving people standard care that they just cannot get because of poor access or that you are holding out in front of them the prospect of possible direct benefit because what you are testing is an intervention that might benefit them clinically.

There tends to be this confusion that I am really helping them because I am giving them the last chance to get treatment for an incurable illness when, in fact, you are offering them something that may work, may not work, statistically probably will not work. And, you know, the recent example of AIDS and immunosuppressive drugs notwithstanding.

So I think what we are trying to do is say you cannot justify risks that are otherwise unjustifiable like pointing to other things like saying, oh, they are being helped because otherwise they would not get any care at all or at least it gives

them the chance of having something that is going to help their illness.

It seems to me you want to say that the risks they are being asked to undergo solely for the benefit of answering the question that will provide no direct knowledge to them, leaving aside whether there is important knowledge about their condition or something. You have to justify those straight up on that arm of the analysis.

PROFESSOR CHARO: Tom?

DR. MURRAY: Alta's example is, I think, a good one. Let's assume -- let's -- one of the problems with any one size fits all scheme is that it has got to encompass the entire world from, you know, the last ditch, you know, touchdown prayer pass with almost no chance of success to sort of routine research, clinical and nonclinical.

I suspect that -- to flush out Alta's example a little bit -- it would be helpful. Let's imagine a study now of where -- let's go back to the inner ear infection. But part of the work up includes a lot of the preventive care and a really good physical exam that that person -- that child would not otherwise have received. That goes on the right hand side.

PROFESSOR CHARO: Why? It does not answer a research question.

DR. MURRAY: Because it does not -- it is not a part of the --

DR. CASSELL: It is a therapeutic question.

DR. MURRAY: -- it is a benefit the child would not have received. And let me -- this -- I may be wrong but it is a benefit the child would not have received had they not been a participant in the research. You are right, it does not answer the research question.

PROFESSOR CHARO: I mean, what I understand -- yes, what I am understanding is it is possible that, in fact, we need to be thinking about three separate lines of components.

DR. MURRAY: Yes.

PROFESSOR CHARO: According to Bernie, and I saw a lot of heads nodding, each line of components needs to be separately evaluated to make sure the risks are balanced by their benefits. Now with regard to the standard care arm that would presumably have already been decided by years of doctors' experiences in a bio-med model.

DR. MURRAY: Excuse me, Alta. That would have been to answer the research question because the research question requires that you end up with comparable groups in both so they do a health screening because they do not want children who are in there with cystic fibrosis.

DR. CASSELL: And malnutrition.

DR. MURRAY: Malnutrition. Otherwise you will have noncomparable groups so this -- interventions designed to answer the research question that nonetheless may have benefit to those same children. So that might count in that right-hand column.

PROFESSOR CHARO: I think it is a stretch.

(Simultaneous discussion.)

DR. LO: Isn't that the problem with the international --

PROFESSOR CHARO: Yes, that is precisely it.

DR. LO: -- studies. We are saying they were not getting any care at all and now they are getting HIV diagnosis, antibiotics for this and vitamins. We are saying it does not justify the fact that --

DR. MURRAY: I am not arguing that, Bernie.

DR. LO: Right.

DR. MURRAY: I am just saying I am just trying to figure out how we would analyze such a study using this scheme before us.

PROFESSOR CHARO: Just if I can go back to what I was saying. It is possible and we will leave it to the staff to figure it out, but we may need to actually add a separate arm. I can come up with other examples where I do not think you could stretch it.

If I understood Bernie correctly you are saying that the risks and benefits should be balanced within each of these arms independently.

And, finally, that the language that is used here having to do with intent and design is probably not appropriate because if something is still at the stage of investigation it is being investigated not with the intent to help people. We may have a hope that it will help people. It possibly could help people, but

fundamentally what is going on is it is being done for the benefit of society and we need to change the language so that we do not emphasize -- we do not buy into the therapeutic misconception with regard to things that have not yet been proven successful.

Is that a fair -- Diane?

DR. SCOTT-JONES: I just wanted to add that it might be more helpful to have the right side more central in how this is laid out because the right side is really what is central. It is the research itself and the second part is secondary. I think as it is -- I think the visual impact of this might possibly inadvertently support the therapeutic misconception because they are there as twin components.

I think the right side is what is central. It is the research. We are talking about research.

PROFESSOR CHARO: So you would like to see something that starts with pure research and then moves on to things that are possibly therapeutic and then things that are really just -- if it turns out to be important to do, and a third which has to do with add ons that are standard care or whatever?

DR. SCOTT-JONES: Yes. Well, yes. If you are going -- you could change this to be the central line down and then arms on the side. I think it is very nice and very sophisticated to look at this issue of the research question, the general question, and very important to look -- to have in here the individuals who are going to be the participants. But, yes, that would be very helpful, too, but also is, as Bernie suggested, the -- that it is

not just offering that benefit. It is the risk/benefit analysis -- potential benefit analysis.

PROFESSOR CHARO: Arturo?

DR. BRITO: Alta, before you brought up your suggestions I had thought about this. I am looking at this left side. Okay. The change in semantics and all that. What if this was written in a way that the components that may impact participants, individual participants, and then within that dividing up potential benefits and potential risks to the participants after you ask the question of research equipoise? How would that fit into your scheme?

Because what I am thinking is to go away from the idea of the therapeutic potential or therapeutic misconception, or what have you, because I think this is one of the problems here, the way it is written. Just to say what can impact, because then within that if you had the components that you described, you know, being in a placebo arm or being in a control arm that does not get the potentially more beneficial treatment, it may help a little bit with that. I do not know. I just --

PROFESSOR CHARO: I am not going to try to answer how -- you know, what I am suggesting would work because I do not know that it will actually wind up being adopted by the staff.

Let me just ask since we need to make sure we get to other recommendations whether there is anything that has not been said that needs to be said before they go back and take another crack.

Trish?

PROFESSOR BACKLAR: They must consider all of the kinds of aspects of research -- genetic research. I do not want you to leave that out of here. We have talked a lot at the table today about social research and clinical research. And we have not -- other than communities, which I thought was trying to bring in the issue of genetic research, I want to make sure that that is thought through very carefully in this model.

PROFESSOR CHARO: I think certainly once we get language that we think works we will definitely have to run it through some scenarios and make sure that it functions the way we anticipate and we will certainly make sure we use a genetics protocol as one example.

Anything else that has not been said in any fashion before they go and take another crack reorganizing?

Okay.

Why don't we move on then to Recommendation 3.3. Another one that I suspect will generate some real discussion on notions of minimal risk?

Comments?

Bernie?

DR. LO: I want to break this one down because one recommendation covers a lot. It seems to me part of what we are saying is what is minimal risk and the second is how does the designation of minimal versus non-minimal affect what happens to it in the IRB system.

So with the first part, what is minimal risk, it struck me in the text that what we are saying is that you cannot -- you want to make it relative only in the sense that what is minimal risk to a normal healthy person may be more than minimal risk to someone who is sick but you cannot run the argument the other way around saying these guys are sick, they get invasive procedures all the time. So if we do a couple of extra spinal taps and brain biopsies they are used to it, no big deal, it is minimal risk.

It seems to me that part of what we are saying is just, you know, restating what I think already ought to be standard of care but I think what people grapple with is this relativism issue and it may be important for us to come up with a very strong statement that relative -- the relativistic nature of minimal risk may mean that you are stricter but you can never be more lenient with people who are patients as opposed to healthy volunteers.

Is that sort of what I think we believe?

PROFESSOR CHARO: Trish, I see you nodded.

PROFESSOR BACKLAR: Yes, I agree. I agree absolutely. I would like to make sure it is very clear.

PROFESSOR CHARO: Bernie, did you find the statement in the text about this being an absolute level of risk as opposed to subjective to be adequate or do you want something stronger?

DR. LO: See, I do not think it is absolute. I think -- I mean, I would like us to -- I propose that we say that what is minimal risk for a normal healthy volunteer may be greater than minimal risk to someone who has a chronic illness, is a patient or

is otherwise undergoing a lot of medical procedures.

But you cannot make the other argument. You cannot argue they are so used to it because they are a patient that it is really minimal risk to them, although for any healthy volunteer it would be much more than minimal risk. So in that sense I think it is relative but it is relative only in one direction and not both ways.

PROFESSOR CHARO: Eric?

DR. CASSELL: First of all, I thought the section defining this was excellent because it did get rid of that business of exposing sick people to greater risk because, after all, other things are done to them all the time.

On the other hand, Bernie, this person who is sick in the every day world would be exposed to a higher level of risk than you want them exposed to in the research setting if you make it --

[Mic feedback.]

DR. CASSELL: -- if they do not -- that happens inside my head a lot, too --

(Laughter.)

DR. CASSELL: -- if you do not make it relative to -- if you do not understand that every day risk is what everybody is exposed to then reducing that for the sick person is putting them in a healthier environment than they would be otherwise. Is that what you want to do in a research setting?

DR. LO: No. I guess what I am trying to say is the

notion of minimal risk can only be stricter for someone who is sick, not laxer compared to healthy people. So it is relative in the sense that it can be tighter for someone who is sick than for a normal volunteer.

DR. CASSELL: But you are not going to require that?

DR. LO: No.

DR. CASSELL: Okay.

DR. MURRAY: Can I ask Bernie a question? One, Bernie, the language in the first sentence of 3.3 captures the -- it wards off the effort to reverse the argument. The language is "minimal risk is the probability and magnitude of harm that is normally encountered in the daily lives of the general population."

I thought that was pretty good language.

DR. CASSELL: Yes.

DR. MURRAY: Now is that adequate for you or do you want more?

DR. LO: No, it is not adequate because the epidemiology -- I am sorry. I am not trying to say something bad about epidemiologists. Epidemiologists regard population as the population of people you hope your study generalizes to.

So in the population of people with HIV, they come in all the time for these procedures. So I think what we --

DR. MURRAY: That is not what this says to me. It says the general population.

DR. LO: Believe me, I have got a bunch of people I know who are going to line up and say this allows me to -- I mean, I

just think -- just put in that adjective saying normal -- the -- I think you want the healthy people to be the norm.

PROFESSOR BACKLAR: Right.

DR. LO: You know, the population has that double meaning.

PROFESSOR CHARO: Bill?

MR. OLDAKER: Yes, I must say that I am a little confused by the discussion, but I think it would probably be helpful if we went through these sentence by sentence and just went through to try and determine whether we agree with that sentence, and I realize they are all interrelated but I think that, you know, I agree that the concept that minimal risk appears to change in people's minds. I think that we want a term that basically is a standard term that applies across the board. I would have difficulty if you had to apply minimal risk differently in different circumstances. I think it is basically the view of the harm to the individual is what we are talking about but I could be wrong.

PROFESSOR CHARO: You know, I understand Bernie's suggestion being that minimal risk is presumptively -- in a biomedical context is presumptively defined as the risk that is encountered in the daily lives of a healthy person in the general population, and that it would have to be adjusted accordingly if the person you were working with as a participant would experience that level of risk as something more than minimal because of that person's own particular situation.

I am concerned and I kind of look to Diane for help here. I am concerned about how to work with this definition in the non-biomedical context. I have no idea what the daily risks of life would be for a normal individual facing socioeconomic and psychological harms and that seems to me to be highly variable. And I am just wondering if you think this definition is going to be workable in the non-biomedical context or if we need to perhaps think about different definitions for different contexts.

DR. SCOTT-JONES: When I first read it I was really pleased with it because it does set a standard for minimal risk that is not relative to the daily life experience of particular subgroups of the population. For example, some have argued that, say, a child who grows up in a neighborhood where there is violence every day and that child faces it every day has a different experience of risk and, therefore, that child can be subjected to research differently from other children. But most people in my field do not agree with that and, in fact, Ross Thompson has written a very nice paper about that and he talks about a standard of decent treatment for children as opposed to some relativistic idea of minimal risk.

I like this as it is very much, but as I was listening to the discussion about the healthy population versus the population of ill people, I wonder if the phrase "general population" could be construed -- the way we sometimes use population we might be referring to say African Americans as opposed to Caucasian Americans. If population can be construed in

that manner I think it is not a good choice but the way I read it, which means people in general, I am very pleased with it but I do not know if there might be the possibility that people would do what you are suggesting is a possibility, Alta, and that is that they say that some people are subjected to a lot of risk in their everyday lives.

PROFESSOR CHARO: No, that actually was not my question. My question was how we evaluate the daily risks of being discriminated against by your employer or your health insurance company and how we evaluate the daily risks of stigmatization.

DR. SCOTT-JONES: Okay. But just to -- let me just try answering again.

PROFESSOR CHARO: Yes.

DR. SCOTT-JONES: That is the point I was hoping to make, and that is that we should not use risk differently for different categories or subgroups of people who may in their everyday lives have more risk every single day. There should be some more general standard of risk and harm that we use for everyone.

The fact that someone lives on a busy street and may be more likely to be run over by a car than another person who lives on a country road is not something that becomes incorporated in the judgment of risk in research.

PROFESSOR CHARO: Larry?

DR. MIIKE: I think that we have to stick with a general definition like this applicable to a population. The way we

should deal with the kinds of words that you have and the kinds of words that you have is this sentence that says "when ethical concerns are raised," and if we can perhaps in the text use those kinds of things as examples of ethical concerns. Otherwise we are going to be sitting here forever trying to figure out a definition of what population minimal risk applies to.

And your example of is discrimination in the workplace part of the general risk, I would say it may be but it is an ethical issue that should not take it back to the level of minimal risk.

PROFESSOR CHARO: Bill?

MR. OLDAKER: Yes, I agree with Larry. I think that you can descend into a counting of, you know, sheep on this. It is difficult. One way that we can deal with it in the future, I would think, is to try and actually give absolute definitions and footnotes some place as to the words we are using.

I think it is -- I think this is a very good statement as I read it over again one more time.

PROFESSOR CHARO: Diane and Bernie?

DR. SCOTT-JONES: I just wanted to say that I believe what I was saying was in agreement with what Larry is saying, what Bill is now saying. I was not saying that we should have different definitions for different groups of people. I like this as it is because it is different from the relativistic statement.

My only concern would be if population means something to other people than what it means to me. Population is a more

inclusive term. Some people use it to exclude.

PROFESSOR CHARO: I think everybody agrees that we do not want to use different definitions in a way that makes people who are already having a hard time vulnerable to even more risky research. That is not, I do not think, a source of disagreement.

The only reason I am -- I think I misled you when I said something about different definitions. I meant different ways of measuring levels of risk when you are talking about physical versus nonphysical harm. I am still struggling with whether or not this kind of definition works for nonphysical harms and it may be that I am the only one who has got a problem with that, in which case I would give up on it.

Bernie, and then Trish?

DR. LO: Excuse me. It seems to me this is one of those examples where the interlocking pieces have to fit together. I do not have a problem with making a definition of minimal risk the way it reads here but then my concern is there are some studies I would do in some populations that I would have very grave ethical concerns about doing in other populations who were vulnerable in other ways.

Now as I was reading through the text accompanying 3.3 I could not figure out what we meant by studies that present no more than minimal risk but nevertheless raise ethical concerns. I mean, one of the ethical concerns I would have, if we take this absolutist definition of minimal risk, is that I think that there are some studies -- and to go after Diane's example -- you know,

with kids who have a lot of other disruption in their lives to do some interventions which will systematically impose disruption may be a much greater risk to them than to kids in other schools that have so much stability in their lives that something that changes may not be a problem.

So I think that again we do not quite get to it in the vulnerability issue either but I think that, for instance, in the International Report and the Impaired Decision Making Capacity Report we acknowledge that there are some studies that you would not want to do with certain populations because the risk/benefit analysis seems to be different for them because of certain impairments or vulnerabilities or just sort of the context in which they live.

So if we call it minimal risk we sort of adjusted that but then we need to have some other way of saying it is not like a minimal risk study with a different group of subjects.

PROFESSOR CHARO: Marjorie, and then Eric and Trish.

DR. SPEERS: I think Alta wants me to clarify something here, which is that the purpose of the minimal risk classification here is simply as a sorting mechanism. It simply is saying whether this study can go through -- in the terminology we are proposing -- administrative review as opposed to a full board review. It is not doing anything more than that. That is the purpose it serves here.

The -- we do say in the text that the IRB -- that an IRB needs to take into account all types of risks when they are making

this classification -- when they are making the determination of whether the study is minimal risk.

So they need to not just consider physical risk but they need to be looking at the psycho-social risk as well. Now maybe we need to make that stronger. This is a case now where we need to put some examples in to provide some guidance.

DR. LO: But see that -- if we are going to sort it on the basis of this absolute definition of minimal risk, I am concerned that stuff is going to fall into the administrative review category that should not be there.

DR. CASSELL: I think it takes care of that, Bernie. It is an "if then" statement. And what -- all those things that you are raising make it fall outside that "if then" statement. All the questions you have make it required -- make it a requirement that it goes for full board review. Anything that does not fit this definition goes for full board review.

DR. LO: I thought what we decided was that we rejected what I had suggested saying that minimal risk may be a narrower concept for some populations than others -- than the general population. It can never be broader but it can be narrower as a way of sort of automatically subjecting those types of research for full board scrutiny.

Instead, if we take a view of minimal risk that says it is going to be relevant to the general population as a whole, not looking at a specific subpopulation that may be more vulnerable, then I think stuff is going to fall into administrative review

that we do not want going there.

So if we are going to do that to -- I mean, I do not care where we juggle. We have to have another criterion for getting into administrative review, which has something to do with the vulnerability of the population that makes them different than the vulnerability of the subjects you are studying.

DR. MIIKE: But, Bernie, we are going to address that in --

PROFESSOR CHARO: Wait, wait, Larry.

DR. MIIKE: -- the vulnerable population area.

PROFESSOR CHARO: Hang on, Larry.

DR. LO: No, because we just said this is a sorting out; that minimal risk all goes for administrative review. Full board does not see it.

DR. CASSELL: No. No.

DR. SPEERS: It may go for administrative review. It would not have to go for administrative review.

DR. LO: Right.

DR. SPEERS: This should be written if it is not to be permissive.

DR. LO: Right. It is more permissive than the current federal regs. Is it not?

DR. SPEERS: It is in that the current federal regulations stipulate that the research has to be minimal risk and fall into one of the nine categories of research.

DR. LO: Right. So this is -- this is -- I am just

concerned. I mean, we have to balance out getting stuff out of full board review that does not need to be there, but also not letting stuff slip through that needs closer scrutiny.

PROFESSOR CHARO: Trish, and then Diane, and then Larry.

PROFESSOR BACKLAR: I think that one of the things that we really have to do because it is so confusing, if it is confusing for us, how difficult it will be for people who are going to look at it, that you are going to have to put this definition of minimal risk in which, Alta, you said a few words before, and I cannot remember them precisely, but you described it exactly as I would hope it would be described, that it did not mean -- maybe it will be caught in the transcript.

But we did not mean by minimal risk that we could do more things to people who were vulnerable.

Some words like that need to be very, very clear and be right here in the recommendation because my fear is that people often just look at recommendations and do not carefully read the text. And I think that we need to make that not just in a box but right in the recommendation what it is we mean by minimal risk so there is no doubt because everybody is very confused about it.

DR. CASSELL: But it also says guidance should be issued.

PROFESSOR CHARO: Eric, can you hold it just for a moment?

Diane?

DR. SCOTT-JONES: I wanted to say that the text does add to what is in the recommendation by outlining what administrative review would entail and it says that it will not be less stringent standards than for a full review.

It is just that fewer people would need to look at it and maybe that could somehow be incorporated briefly in Recommendation 3.3 so that it is clear to someone who is only looking over the recommendations that administrative review is not just a renaming of the old expedited and exempt categories but it is still going to have a thorough appropriate review.

I think that would help a lot to allay some of the concerns that Bernie has but I still am struck by the importance of what Bernie said and what Bernie is saying about wanting a relative standard is different from the way most people use it. Most people use it to say that you should not have as stringent standards for some groups of vulnerable people. Bernie is saying the opposite that there are some groups of vulnerable people who need a little bit more attention and that what is okay for us in our everyday lives might not be okay for some vulnerable groups.

I think that is a worthy point. I do not know how it could be easily incorporated here except to rely on the judgment of the people who would be making the review but I think that is a very important point that we should not lose sight of.

PROFESSOR CHARO: Larry?

DR. MIIKE: I wanted to address that point because when we started this meeting Bernie had mentioned something about we

have not addressed vulnerable populations, and we do. We extensively addressed this in a report taking an analytical approach which would include all of the categories of participants that you would be worried about and Bernie would be worried about.

And this is not the place in which -- maybe we can reference that the application of the minimal risk review may be affected by -- would be affected by another section of what we are proposing, which is special treatments for vulnerable populations.

I mean, I think that is where we are going to be addressing them because, you know, we cannot include -- well, that is enough.

PROFESSOR CHARO: Okay. And I apologize but I am trying to take note of the time. It is 10:15 and we did want to get through Chapter 3 so I am going to ask if Eric and Arturo and Bernie --

DR. CASSELL: I have said it all.

PROFESSOR CHARO: Okay.

DR. CASSELL: I think that they are good recommendations.

PROFESSOR CHARO: Arturo?

DR. BRITO: Just very quickly. This goes back to Recommendation 3.1 and what Bernie is saying.

I think it does need to be included in here, this protection, and I think a way to take 3.1 and combine it in here where you are discussing the guidance -- here is one of the areas

where guidance can be -- it can be -- very valuable is with how it may affect communities and vulnerable populations. So somehow taking those two and combining them in here, I think -- that is a suggestion.

PROFESSOR CHARO: Bernie?

DR. LO: Let me try and tie in with what Diane was saying. What concerns me about administrative review is the fewer people that look at a study, I think, you diminish the chance of someone saying, now, wait a minute, this may be true for you and me, but for this population -- or it may be true for the rest of you but let me tell you where I come from. I do not think that is minimal risk.

And part of -- it seems to me -- a part of the reputed strength of the IRB is the diversity of views, the lay members, the community members, who can point out issues that are particularly germane to a specific population.

A specific subject -- group of subjects to be studied that would not be obvious to a smaller group of people, particularly the types of people who might be doing administrative review. That is my concern.

PROFESSOR CHARO: Bernie, I think that your concerns can probably be answered in the next draft with a kind of algorithm in which the inquiry begins with whether something would be minimal risk for the general healthy well-situated population.

And then the next question is would it still be minimal risk or would it now be riskier than that for the particular

participants that are proposed in this protocol.

And if the answer to that question is, yes, it would be more than minimal risk to them, it goes to full board review. And it -- and that way it cannot fall through the cracks but that is just a little -- it is a little algorithm you have to go through.

Okay. All right.

Let's move on then to Recommendation 3.4. And any comments here?

Bill?

MR. OLDAKER: When we talk about the central office here I think that we are talking about it being empowered to issue regulations which would accomplish what we are saying here.

So I am not sure the word "revised" is proper here but -- you know, so I am not sure if we want to say empowered or should have the authority. I mean, it is a technical point. The other thing is, you know, I think the word "dissolve" -- I think what we are talking about in reality is that we want them to substitute administrative review for the prior concept of the use of exemptions. Right? I agree with -- I am just trying to make the --

PROFESSOR CHARO: Good.

MR. OLDAKER: -- the exact.

PROFESSOR CHARO: Thank you. Diane?

DR. SCOTT-JONES: I think it would be great to add some of the phrases in the text to Recommendation 3.4. It is very nice and short as it is. If we could add something about not applying

less stringent standards for approval as is on page 19, I think it would help because as it is, someone who is looking to minimize the duties or responsibilities of the IRB might think that the new administrative review would simply be no more than the current expedited or exempt so I think it would be very nice to add.

PROFESSOR CHARO: Anyone else? Larry?

DR. MIIKE: I have some concerns about eliminating all together the exemption process or the exemption category because we are saying administrative review is actually the full review by fewer members and I can see just greatly increasing the burden on IRBs for doing this.

On the other hand if we had kept exemptions I would have proposed that it is the IRB that grants the exemptions, not some anonymous official in an institution so we would have consistency. So I do not know whether that would diminish the work.

But in order to diminish the work I think that we need to say later on in the back end about monitoring and evaluation that, for example, I cannot see the IRBs or whatever mechanism being set up establishing monitoring for projects that are brought to administrative review, which has really no risk whatsoever and are really not controversial topics.

So I am trying to find a way of avoiding a front end burden but if we want to impose that front end burden we should remove the back end burden from it.

PROFESSOR CHARO: Are people comfortable with the elimination of exemption as a concept because that is an important

element here? Bernie?

DR. LO: No, I actually support Larry. I think the problem with exemption strictly defined is that the investigator exempts himself without having anyone else look over their shoulder and to me that is very different than a full review by fewer people. It is just someone to look at it and say, yes, this really is a question to study or this really is such and such type of study.

DR. SPEERS: Let me ask a question about exemptions. There seems to me to be three issues with exemptions as they now exist. One is who makes the determination. Two, if something is exempt, it is exempt from the federal regulations, not just from IRB review. So it is exempt from the requirements of informed consent or minimizing risks as we have said.

And, secondly or thirdly, the exemption categories now do not say anything about the level of risk. So that because the exemption categories focus on methods, it is possible to have a more than minimal risk survey, for example, in adults meet the criteria for exemption.

Now do you want -- if you keep exemptions do you want to keep them with those same criteria or do you want to change those criteria for making the exemption determination?

PROFESSOR CHARO: Bill?

MR. OLDAKER: I am in favor of the language you have here. I think it is far better to have an administrative review which empowers the IRB to make a decision as opposed to the

exemption process which takes people out from under the law entirely. I think that when we get to enforcement, I think we can talk about how these decisions can be enforced but I think that I would far prefer to see people covered under all circumstances and an exemption process by definition takes people out from underneath the authority of the regulations.

PROFESSOR CHARO: Bernie?

DR. LO: To me it is a matter of semantics. I support that the IRB should -- if there are going to be exemptions it should be the IRB that has to review it and not some more subjective place. But then the question becomes what happens after the review? Do you then say, oh, that is always exempt, no longer subject to the Common Rule or whatever federal regulatory process? Or that it is such a noncontroversial project that our initial review is enough and, you know, we do not need to deal with it anymore.

PROFESSOR CHARO: Bernie?

DR. LO: Let me first ask a question and give you some examples. First, it is not clear to me that the current federal regulations allow you to exempt survey research on adults that is not minimal risk.

Aren't there concerns about how -- aren't there clauses in the current federal regs saying that survey research cannot have any risk of damaging the subject's economic standing, legal liability, reputation, all that sort of stuff?

So it is hard for me to imagine -- I mean, the kinds of

research I would not want to be exempted are things that have to do with drug addiction, sexuality, AIDS, mental illness, and at least as the regs are interpreted at my institution that stuff is not exempt in survey research. It has to go through expedited review.

The second thing about how -- what does exemption mean at the back end? What it clearly means at our institution is that there is a mechanism that if any problems come up the IRB gets involved.

So subjects have complained about so-called exempted minimal risk research usually having to do with how did they get my name. How -- why was I approached in this matter? And at least then the IRB keeps enough of a hand in the pot that they are willing to get involved and make it known that they are the correct people to get involved and so forth.

So again it is a matter of -- but I am concerned, I must say, that IRBs are really overworked and their staff is overworked so I do not know who is going to be doing these expedited reviews.

Exemptions at our institution are much briefer form. It is basically a checklist of questions. Are you doing any of the following? Well, if you are, you are not exempt. So it does not -- you do not have to write that. You know, even that little two page summary of your protocol, investigators hate it, it is much more difficult for the IRB staff or IRB chair to review, and so it is a substantial amount of work on an overburdened system,

and I -- you know, I -- we are going to be asking IRBs to do a lot more than they are now doing.

I think it would be nice if we could be careful that everything new we are asking them to do really, really counts because the current criticism is they get bogged down in stuff that is just not that important, the so-called bean counting. And I think anything we do that adds to that will undermine our credibility.

PROFESSOR CHARO: For the sake of trying to move along this morning, may I suggest that we keep this discussion in mind as we go through both Chapters 4 and Chapters 2? Chapter 4 and Chapter 2, both of which play into the role of the IRBs and try at the end of this two days to give some clear guidance about how we want exemptions to be handled.

It may be easier when we see it within the larger infrastructure that is being proposed to make a final determination. So if I can just say that if we can just hold this for a moment and we are to Recommendation 3.5.

We have got five minutes before our scheduled break. Why don't I just ask whether people -- get a sense of whether or not 3.5 is controversial and see whether or not we might be able to make some progress on it before the break.

3.6? I feel like I am at --

(Laughter.)

PROFESSOR CHARO: 3.6.

PROFESSOR BACKLAR: There is an ethical problem right

there.

(Laughter.)

PROFESSOR CHARO: Going, going --

DR. LO: Fifty cents.

(Laughter.)

DR. CASSELL: Keep going.

PROFESSOR CHARO: 3.7? Oh, I am sorry. 3.6. Oh, we have a late bidder on 3.6.

DR. LO: As I look at 3.5/6/7/8, those are all informed consent related. And it strikes me that one of the things I was hoping we would do in this report is to say, you know, all the emphasis on consent forms is misplaced. We have to look more at the process of consent and not just at the consent form.

I am not quite sure how that translates into a recommendation but I do not really see that in this set of recommendations on this page and I would like us to try and, you know, use our report portion in that direction.

DR. CASSELL: It certainly says it in the text.

PROFESSOR BACKLAR: It does say it in the text and again when people only look at this it is a problem. You need to see it in the recommendations, too. I agree.

PROFESSOR CHARO: Bernie, can I offer you a friendly amendment then in 3.5? The central office should issue regulations that deemphasize the consent form and focus instead on the process of...would that make you feel like it got front and center attention?

DR. LO: That, and then I think the other things we have said elsewhere are that IRB in some circumstances may want to do more to actually observe the consent process. I mean, all the things that we did, for example, in the decision making capacity report. Sort of a menu of added protections in certain circumstances, which involve really sort of direct -- more direct monitoring of the consent process.

PROFESSOR CHARO: So you want some of that pulled out of text and -- once again at the very end of all of this we will get a chance to look at the whole range of recommendations and we will get back to Larry's point about, you know, variations in terms of generality versus specificity and we will see if we are comfortable with what emerged.

So 3.7, which is consistent with what we recommended in the international report.

DR. CASSELL: Yes, it is consistent. It seems to me to be consistent.

PROFESSOR CHARO: Okay. I would like to propose we take a 15 minute break and come back because 3.8 has to do with the regulations that we are proposing for waiving informed consent that might actually generate a little more discussion but why don't we resume at 10:45?

(Whereupon, a break was taken.)

PROFESSOR CHARO: Okay. We are going to move on to Recommendation 3.8 focuses on waivers of informed consent. Something which we have had to address in other reports as well

and the text does a nice job of reminding us of the other circumstances where we have had to discuss whether or not we like the current system or some variation on it.

So let me ask people for their reactions to the current proposed recommendation.

DR. MIIKE: There is none.

PROFESSOR CHARO: Larry has no reaction.

Bernie?

DR. LO: I like -- we are on 3.8, right? Yes. I like 3.8 because I think that it is clearer. It extends the waiver issue to places where it ought to be extended. My only suggestion would be to suggest I am not sure it is the central office -- there should be certain presumptions that certain types of things in general are going to be eligible for waivers of informed consent as we did with the human biological materials.

Just to sort of carve out general areas to say, okay, guys, you know, you do not really need to be getting consent forms for these. Health services research I think would be another one under certain circumstances.

PROFESSOR CHARO: Other reactions?

I would like to say that -- oh, sorry, Bill?

MR. OLDAKER: We use in the -- on line 20 the term "minimal risk" and then in line 29 "dignitary harm." I assume that when we are thinking about minimal risk here we are not talking about health risk, we are talking about other types of risks but I am not sure.

DR. SPEERS: When we are talking about minimal risk here, we are talking about it as we have defined it so it is the types of harms that are encountered as part of daily living, which could include some types of physical --

MR. OLDAKER: Health risks?

DR. SPEERS: Yes, health risks.

MR. OLDAKER: Thank you.

DR. SPEERS: Can I just make one statement?

PROFESSOR CHARO: Please.

DR. SPEERS: I just want to make sure certain that this part is clear to everyone. Based on the way that the text and the recommendations have progressed through this section on informed consent, this waiver is for waiver of informed consent.

It is no longer for a waiver or alteration of informed consent because we dealt with the alteration issue by saying that what is in a consent -- in the consent process should be tailored to the particular type of research and the needs of the prospective participants. So this is only dealing with waiver of informed consent.

PROFESSOR CHARO: I would like to ask people's reactions to something that struck me when I was reading it and it had to do with the second criterion that the waiver will not adversely affect the rights and welfare of the participants.

Now we had very lengthy discussions during the drafting of the human biological materials report about what that phrase ought to mean. We managed to come up with a plausible

interpretation of that phrase but it was difficult to come up with that interpretation.

The word "rights" was not terribly complicated because we understood that people may have certain rights given to them under other federal or state law or even, we said, their customary practice, although I might have limited it to law just for clarity sake, and that certainly you could not waive consent where it was something people had a right to exercise under a different law that was not preempted by these regulations.

I remember struggling mightily with the notion of welfare because we had already in the first criterion said that the study involves no greater than minimal risk. And in this particular report we have now included in the notion of risk not only risk to the participant but risk to others.

And in the HBM report we gave meaning to the word "welfare" by focusing on risk to others and said does the risk to others constitute some threat to the welfare of the participant and in that way we tried to capture people's interest in, for example, being able to politically oppose the probable uses of study results.

But here now it seems somewhat superfluous since we have incorporated notions of risk already through 3.1, incorporated notions of risk to others in 3.1, and I just fear once again confusion about the meaning of the word "welfare" so I would ask just for either feedback as to what that term ought to mean as used here that is different than what has already been described

elsewhere or whether that word should be dropped out and we should it limit it to "rights" just for the sake of clarity since IRBs will struggle mightily on this one as well.

Tom?

DR. MURRAY: I would be in favor of keeping the language as it is because "rights" refers to one set of potential violations and "welfare" we have heard in a broad way to the consequences of many kinds, even those that would not be straight forward violations of rights.

PROFESSOR CHARO: I agree but in what way would welfare be different from the risks that are referred to in the first criterion, which would presumably cover the risk of stigmatization, the risk of discrimination, the risk of embarrassment as well as any physically invasive -- you know, risks that come from physical invasion.

So how is welfare different from one so that we can make it easy for people to understand what we are trying to do here?

DR. MURRAY: I cannot think of a case off hand that would not fall under minimal risk but that would concern welfare. I would still be in favor of keeping it in for two reasons. One is sometimes the belt and suspenders is -- both belt and suspenders is perfectly acceptable and wise. And, secondly, it is a phrase that has a kind of echo of familiarity to it that I think people can assign meaning to it and interpret it meaningfully. To have rights stand out there nakedly without welfare attached to it in this room would be a bit odd and would strike many people as a

bit odd.

But I do not feel strongly about it.

PROFESSOR CHARO: Other reactions?

PROFESSOR BACKLAR: I agree. It is rights and welfare. Welfare encompasses interests as well as -- rights encompasses interest but so does welfare and well-being. It has many connotations. I would not wish to drop it.

PROFESSOR CHARO: I see other people nodding their heads that they want to keep the language. Then is there any way that we can give it some more substance in terms of guidance so that there is no room for confusion and this does not become an obstacle to waiving consent under circumstances where we think it is appropriate?

DR. MIIKE: I see your point in the sense that if we are going to delete "welfare," I would also delete "rights" because one and two are really as we define minimal risk are redundant so it is a question of do we want to feel good about it and leave the whole number two in or do we simply drop it as a criteria. Although it may be more difficult to then implement because then we would expect people to understand what we mean by number one about minimal risk as incorporating all those kinds of elements.

PROFESSOR CHARO: Diane?

DR. SCOTT-JONES: I would want to leave in rights and welfare because we cannot anticipate the circumstances under which persons -- investigators will decide that they should be able to waive the expectation or requirement of informed consent and so I

think we should have language that includes possibilities and I think rights and welfare is a commonly used phrase that is used in our -- I think it is used in our charge to us as a commission for what we are supposed to be about and I would go for leaving it in because we cannot anticipate all of the kinds of circumstances under which investigators will decide that they should be able to waive and I think it would -- I think it is appropriate to leave it in.

PROFESSOR CHARO: Jim?

DR. CHILDRESS: I think I am more inclined in Alta's direction and I guess I would be helped by some indication of the kinds of things you might have in mind here that would not be captured in the context where we are saying no greater than minimal risk is involved. So that would be helpful to me so it is really echoing Alta's question to all of us.

DR. MIIKE: May I ask a procedural question?

PROFESSOR CHARO: Sure.

DR. MIIKE: As contemplated it would be the current way in which the investigator decides that I did not seek informed consent because of the following reasons, et cetera, et cetera, but the IRB reviews that reasoning, right?

PROFESSOR CHARO: Correct.

DR. MURRAY: I would reverse the presumption and say explain why we must take the "welfare" out of the second? Again, it is a phrase that most people will recognize.

PROFESSOR CHARO: Here is what drove the concern but I

do not want to take too much time on it because I am aware of the fact that it is already 11:00 a.m.

On our own IRB we have received requests for waivers of consent and have determined that the research was minimal risk. It frequently would come up in the context of either survey or research with tissue or research on medical records. We would determine that it was minimal risk because the nature of the information that was being sought was not the kind of information that would implicate somebody's social status or their employment status or their health insurance status, et cetera.

We determined that there was not applicable state or federal law that prohibited the waiver of consent and we had determined that it really was going to be logistically nightmarish to try to go back to all the individuals and individually query them for personal consent but we spent 42 minutes on welfare and we were discussing whether or not there was an intrinsic invasion of privacy that was involved in going back to these materials or records and whether that was in a sense the kind of harm that constituted adversely affecting somebody's welfare.

Mostly what struck me about the discussion is that we just did not know what the word meant and when we discussed it during the HBM meetings we continued to not be sure what it meant so, I guess, it is a very selfish desire to know what we are supposed to talk about when we are sitting on an IRB.

If we know what we are talking about then there is no problem with leaving the word in. If we do not, then we risk

these kinds of long discussions.

DR. MURRAY: May I make a suggestion just to serve the purpose of getting today's meeting going that Alta's proposed revision be a challenge for us over the next couple of weeks to try to articulate the case, you know, do it by e-mail or maybe staff could draft something that would allow us to work through whether we think there is added value either because in that second point "welfare" means something other or more than minimal risk.

PROFESSOR CHARO: Right.

DR. MURRAY: Or we think even though it was essentially redundant there was value in keeping it in nonetheless but we probably could spend an hour talking about it today but --

PROFESSOR CHARO: That would welcome because, you know, I suspect that it may turn out that in the end rights and welfare is really the general language and all these other things are the way in which we inform those words that you can waive consent where it does not affect rights and welfare, and we know that it does and when, and then we have our list. I mean, it may just be what is general and what is a criterion.

DR. MURRAY: It seems to me an exercise well worth doing and we probably should have some time to reflect on it rather than --

PROFESSOR CHARO: Larry?

DR. MIIKE: Can I also suggest that we consider removing it because anything that adversely affects the rights and welfare

of the participant is not minimal risk?

PROFESSOR CHARO: I think Tom's suggestion that perhaps we continue to try to figure out what we are trying to accomplish here and what order of words and what is criterion and what is general might be the way to handle it over time.

3.9? Reactions?

Jim?

DR. CHILDRESS: Yes. I have serious problems with this as a conceptual matter because privacy, if it -- whatever it refers to, it does not refer in the first instance to interest and I -- it is a state of affairs in which there is limited access to a person, their privacy rights, their privacy interest and I would prefer to say that -- first of all, I am not sure why we need a clear cut definition here in the first place because what we are really interested in are the interests and the protections, and privacy here is defining the terms of interest, confidentiality in terms of protection, and I guess I would prefer to say if we are going to stick with the interest approach that privacy interests are a person's interest in controlling access of others and so forth because this is not a definition of privacy. It is a statement about a particular kind of interest.

PROFESSOR CHARO: Other comments? Yes, Bernie?

DR. LO: It strikes me that we may want to say more than just we should have some clear and comprehensive definitions. We may also want to say that somebody, whether it is the central office or local IRB, ought to make available to investigators a

list of techniques for enhancing protection of privacy in certain types of research where it is a main issue, particularly health services research and survey research.

So what I think is often lacking is a sense that you have got to do more -- I mean, is this boiler plate that everyone puts in their IRB submission that we are going to have a code. It is stored separately from the data. It is kept under -- it is in a locked storage cabinet and only the investigator and research team has access to it and that is supposed to be all there is about privacy. It leaves out lots of things about encryption, coding, merging databases, whether you leave computers hooked up to the internet, whether you can take a disk home with you.

So I think there needs to be a much more sophisticated notion that you can do an awful lot to protect privacy and protect confidentiality and so on and, thereby, minimize the risks and maybe even make it minimal risk research, and those techniques are not generally known and appreciated. The IOM report on protecting privacy in health services research, you know, one of the things we tried to do is to give it sort of a comprehensive overview of the types of things you can do and I think that kind of practical guidance would go a long way to enhancing the protection of privacy and making it easier for IRBs to review certain types of research.

PROFESSOR CHARO: Bernie, in the second sentence of Recommendation 3.9 it asks the "central office to issue guidance describing, as it puts it,concerns and threats to privacy and

confidentiality and ways to protect them." Are you suggesting that this should have added detail about what should be in those guidances?

DR. LO: Well, I think in the text it would give -- I actually think the main thrust of the recommendation ought to be you ought to provide the guidance, not the definitions.

PROFESSOR CHARO: Okay.

Tom?

DR. MURRAY: Well, I think this recommendation as it stands before us is certainly in the right direction. What I am hearing are two things. One is that the definitions -- certainly the definition of privacy may need to be refined. I believe that was the thrust of Jim's comment.

And, secondly, that the guidance is central here or the recommendation that we need a better phrase than central office, that the agency should issue guidance. Here I would like to break things out into a multi-point recommendation where we describe -- I am not sure what concerns and threats is meant to embrace here or meant to encompass but something about concerns about privacy if it is different from threats to privacy and confidentiality and means to protect confidentiality.

And it might be -- one might call it just -- otherwise they tend to get lumped together and we are really asking for a great deal in this recommendation. I think it is a very important kind of thing -- it is very important guidance and it might just be helpful to pull them out and bullet them so that they do not

get subsumed.

PROFESSOR CHARO: Eric?

DR. CASSELL: Well, I -- my comment is really much in line. I would take out the definitions. In one way they are too narrow and we cannot make an adequate definition that really covers all the things we really want people to do and I think the guidance part really covers that. We want people to understand what privacy is and what confidentiality is. They are two largely breached areas of human interest and they ought to be covered in depth.

So, also, I also think we should start calling it something besides the central office. I had in my head the office responsible for the protection of human research participants. I do not care how long the word is. So we do not get caught up in --

PROFESSOR CHARO: May I suggest the acronym and we can use the acronym?

DR. CASSELL: Well, but the trouble is if we use an acronym somebody is going to start funding the acronym, you see, and --

(Laughter.)

PROFESSOR CHARO: Larry?

DR. MIIKE: I will make a suggestion about the issue about definitions and the guidance issue. We should reframe this recommendation in terms of guidance and say it is guidance in controlling the access of others to the -- in other words, use

this definition as the statement of the guidance and then you would finesse it and having to actually define privacy and confidentiality because that is what we want to do.

PROFESSOR CHARO: Okay. Bill?

MR. OLDAKER: Well, as I understand what we are doing here we are making recommendations, number one, for whatever we call it, the Office of Bioethics or whatever it is, to be established, which will take legislation I would think. Maybe not. But -- and then we are suggesting that this organization be empowered to write regulations on these topics and so I think anything more than basically giving them kind of a broad overall direction about how they write those regulations, well bottom line, what we are basically doing is trying to get a group empowered to deal with these issues in a comprehensive manner.

PROFESSOR CHARO: Right.

MR. OLDAKER: So I think this is fine but I think it could also be shortened in the way that Eric suggested and we just deal with privacy and confidentiality as two things that have to be covered.

PROFESSOR CHARO: Okay. 3.10, which talks about one of the important elements of how one can protect confidentiality. Comments, response? Isn't it 3.10?

DR. MURRAY: 3.10?

PROFESSOR CHARO: Yes, 3.10.

DR. MURRAY: My only -- I think this is right on point. My only -- it would be grammatical. I would probably rewrite it

to say "Congress should pass legislation authorizing stronger legal protections of confidentiality that prohibit investigators from releasing identifiable data and that protect investigators from compulsory disclosures." Just make it more active rather than passive.

PROFESSOR CHARO: Bernie?

DR. LO: I have concerns about legally mandated disclosures. We talked about this a little bit in the text with child abuse and reporting of sexually transmitted diseases and I think we need to have some tightening in the language to not -- to allow researchers to fulfill an already mandated recording requirement.

DR. SPEERS: Let me comment on that and know what it is you want to say about that because I am familiar with the -- some of the federal statutes of protecting confidentiality as well as the certificates of confidentiality. They are not consistent with respect to what must -- what is mandated so that child abuse is not always interpreted as being a mandated reportable condition.

So I think you would have to first say something about whether there are certain conditions or situations that you think are an absolutely must be reported and then we could go on to say that that needs to be part of this recommendation.

DR. LO: Yes. Well, I mean, this opens up a whole vista of issues but researchers come to me and ask, "I am doing a study on mental illness and I am identifying people who are suicidal. Isn't it my ethical obligation to intervene and get them some

help. I have people who are threatening identified individuals with a serious threat of harm." Now then there are -- so those may be ethical obligations and maybe some case law.

Then there are situations in which people say, "Don't I have a legal statutory obligation in our state to report child abuse, elder abuse, which predictively I will locate in this study because I am asking questions directly relevant to that?"

So I think we need to sort of sort through whether -- I mean, I think what we are doing here is trying to protect against disclosures that the investigator does not believe are acceptable overriding instances where it is acceptable to override confidentiality but then there are another set of categories where I think investigators feel it is their ethical and legal duty to override confidentiality and it seems to me we ought to be trying to separate out those issues.

PROFESSOR BACKLAR: And the issue there, of course, is when you are doing -- starting the study and you have to inform it is part of the informed consent that there are certain areas that you may have to report.

PROFESSOR CHARO: Let me just add to the nightmarish mix here and focus it only on situations where the investigators are compelled to reveal information that they have gathered during an investigation. We have a federalism problem here because we are talking about federal legislation being enacted that might or might not be interpreted to somehow preempt state laws that go to reporting requirements typically on child abuse, sometimes elder

abuse and sometimes domestic violence of adults, sometimes gunshots, sometimes HIV or other infection disease status.

And it is not immediately apparent to me that this is an area where such federal preemption would easily be upheld since there are strong state interests at play and one would have to make a very strong argument about the desperate need for uniformity across the country in order to support the preemption of state laws.

There are different approaches we could take here. One is to acknowledge that such state laws exist and that where they exist that investigators and IRBs would be well advised to negotiate with state authorities on a protocol by protocol basis to see if they can get out from under such reporting requirements and that the state authorities are convinced that the long-term gains of allowing the research to go forward with the best possible data being generated due to complete confidentiality would be ultimately to help reduce the incidence of whatever it is they are concerned about.

Well, the state authorities may say no and it may be that the research cannot go forward without telling people that they are at risk of being reported and that was circumventing the quality of the data. That is one approach.

The second is to take a very hard line and say you want to try to preempt the states and go for it and the third is to leave it in the muddle that it is right now as IRBs struggle with it individually.

Tom?

DR. MURRAY: There is an existing mechanism in the certificate of confidentiality but I took it to be permitted by federal law and I wondered how that -- just informationally how that dealt with this issue of federalism.

PROFESSOR CHARO: Marjorie, do you want to go through some of the details of it?

DR. SPEERS: A bit. I will try to. The certificates of confidentiality are issued to institutions through -- generally through one of the departments in HHS. The guidance that the department uses and the various agencies use in issuing certificates is fairly vague language. There is a lot of interpretation that occurs among the agencies that issue these certificates.

With respect to what has to be reported, my recollection is that the language is vague or silent on it so that you could have two types of certificates issued. One certificate is to say that cases of child abuse, for example, will be reported. And in another one where cases of child abuse would not be reported. That is the kind of flexibility that exists now in the certificates.

DR. MURRAY: How do they deal with the federalism issue that Alta raised?

DR. SPEERS: I am not so certain that they do in the sense that when they are offered -- I am unclear how the process deals, for example, with local state law or how that is taken into

account.

DR. SCOTT-JONES: In the text on page 38 it says that DHS regards the certificates as superseding state law so I do not know what has happened in practice or whether there has ever been an issue but there is a citation of case law supporting DHHS position.

DR. SPEERS: I am sorry, and that is the only case that we know about. Yes. Our statements in there are both true as to how the department views it. Whether that is correct, there has only been as far as we know the one case in New York.

PROFESSOR CHARO: Because they are issued so sparingly and because they have not been tested against the full range of criminal and civil contexts. There is a kind of lingering nervousness and even when certificates of confidentiality are used typically participants are informed that that certificate of confidentiality is not fully understood. And we are not really sure what guarantees you accept but it will be even harder for them to get the stuff but we still cannot promise that we will never get the stuff. We have never been able to write a consent form or have a discussion in which we actually guaranteed confidentiality.

Bill?

MR. OLDAKER: This is -- we have gone through this. I think these are very difficult questions and I think that, you know, kind of gave a multiple choice of number three being muddled. I think to a certain extent, you know, we do not want to

muddle down but I think we want to leave to Congress the ability to determine these issues because they are going to do it anyhow and whether it is preempted or we are looking at various parts of state law which are going to become very relevant where disclosures have to be made from, you know, child abuse to elder abuse, and even some states with mandatory reporting on drug addiction or taking drugs.

I do not think those are things which we can adequately deal with in the amount of time we have. I think we would be better off to point out in some way that those are issues and just let those be resolved as they are going to be resolved. You know, they will be resolved on somewhat of a political basis by powers which are beyond ours.

But I think we do want to make sure that the overall recommendation is except in those cases where confidentiality is protected.

PROFESSOR CHARO: Larry?

DR. MIIKE: I do not think we should have a recommendation in this area and the reason is that we are not talking about absolute confidentiality. We are talking about protecting confidentiality and the patient's consent for release of confidentiality. And commonly the way you deal with it is you say in the consent form we have these procedures for confidentiality. However, the FDA may subpoena the records if you are part of a clinical trial. State laws may do this and this. The court may come in and do this and this.

So I do not see why we need to have a recommendation that moves towards almost an absolute confidentiality basis when the issue here is consent and reasonableness in confidentiality and letting the participant know when absolute confidentiality is not assured. And as long as they can participate knowing those kinds of things I think that is adequate to protect the confidentiality basis and their participation.

If we try to push legislation like this it gets into such a morass that we are already talking about that I do not think it is going to make any sense for us to try to address it in here.

And then it also -- just in terms of the way that these recommendations are put forth, here are coming along things about a central office and then all of a sudden there is a very large one. The congress should pass legislation.

So for both from a substantive and a procedural thing I think we should just eliminate this recommendation.

PROFESSOR CHARO: Tom?

DR. MURRAY: Well, I would actually be in favor of a strong recommendation on this issue, Larry, and let me tell you what my reasons are. There are -- there have been and will continue to be efforts to -- harass is not too strong a word -- to harass researchers and possibly even to intimidate prospective subjects on issues concerning research where the issue might affect the matter of public policy.

We have seen this in the tobacco litigation where

researchers were pummelled by lawsuits requesting raw data and such. We have seen it in other issues about public health. We will see it in issues about health and environmental matters.

And I think to give -- and one should not under estimate the amount of pressure and intimidation that can be exercised by bodies with lots of money and strong motives to prevent or intimidate or disrupt certain kinds of research. So I think I have that in mind as one of the things I am thinking about when I am in favor of strong congressional protections for privacy and confidentiality.

DR. MIIKE: I am unconvinced.

PROFESSOR CHARO: Reactions? Bette?

MS. KRAMER: Well, I would go along with Tom and this was a big issue when we were doing the HBM report and we were considering privacy and confidentiality issues around genetic research in particular. So it seems to me that this is something that is going to become more of a problem as we go forward from this time and I think it is important that we make a recommendation, a strong recommendation along these lines.

PROFESSOR CHARO: Bernie?

DR. LO: We may want to distinguish between things where we really want to make a recommendation because we really know what we are talking about or convinced of and other issues where we want to raise a big flag that this is an important issue and we do not have all the answers. The clock is ticking. We are not going to be able to figure it out although we are pretty bright.

Someone else needs to think about this and we are just saying pay attention, this is a big issue.

Let's not try and solve things where it is unlikely we are going to come up with the right answer in the time we have left.

PROFESSOR CHARO: And that would suggest, Bernie, what exactly?

DR. LO: Just having a nice paragraph saying these are important issues for all the reasons Tom raised and Bette raised but to say that this is complicated. A lot of people need to chime in. We do not have all the answers. Part of the solution has got to look like X, Y and Z.

DR. MESLIN: So you would get rid of 3.10?

DR. LO: Well, you know, there is a lot of other pieces of the puzzle in Congress doing this. I mean, investigators need to think through what are the confidentiality issues. IRBs need to press them, have you thought this through beforehand, what are you going to do when you get this information. You have to be willing to go to bat to quash a subpoena if you have -- there is a lot of other -- know about -- there is a lot more. And to say congress should do it kind of, you know -- congress in their best wisdom is going to do what they want to do. IRBs and investigators are much more likely to listen.

PROFESSOR CHARO: Would the resort to the passive tense be a solution here, Bernie, in which there would be agreement that there is a strong statement that better methods for ensuring

confidentiality of data are very much needed in an era of more and more databases being developed in more and more areas in which this information can be used and that would direct the attention of -- and without saying that it has to be either federal legislation or federal regulation or action by the states or the model laws or whatever?

DR. LO: That is part of it but I also think there are justifiable exceptions to confidentiality which are carved out and some of them will happen in the research arena and we have to kind of have investigators and IRBs work to sort through what are the types of things we are going to say, no, this is really confidential and the sorts of things that, no, overriding confidentiality is subject to certain conditions about, you know, releasing only minimal data and stuff is probably on the whole a better approach.

PROFESSOR CHARO: Trish and Tom?

DR. LO: So it is not just strengthening confidentiality. It is making sure investigators know that there are some times when they are going to ethically want to disclose.

PROFESSOR CHARO: Trish, Tom and Bette.

PROFESSOR BACKLAR: I think one of the issues that really is of some concern, though, is that if you -- is the -- is that there is some over arching understanding that it does not move around from state to state. I do think there is some importance of some kind of federal regulations so that research -- when you have multi-site research protocols and some states have

certain laws and other states have other laws it is very, very confusing and very difficult. So I do think you do want to look at something that could be useful for researchers nationally, not just state by state, and that is, I think, a big issue.

PROFESSOR CHARO: Tom?

DR. MURRAY: I hate to be wishy washy on this point. Granted I certainly do not have the wisdom to tell you what the legislation should say. I do not even have the wisdom to say that it should be congressional legislation rather than some rule making although my inclination is from what I know I think legislation is the route to go.

I would be in favor of a pretty strong stand here. And it does not -- Bernie's comments about, well, there will be subtleties there, of course there are, and Bill's comment about it will be hashed out in the political process, I fully understand that but I still think it would be useful for us to take a stand to say that it would benefit research and it would benefit people who participate in research if there was a much clearer and stronger federal law and policy about confidentiality and privacy. I think that is what the recommendation is attempting to say and I would want to put forward such a recommendation.

PROFESSOR CHARO: Bette and then Marjorie?

MS. KRAMER: When you listen to Bernie and others around the table talk about how it ought to happen, that is all fine and dandy but I think -- I mean, one of the points that we make is that research is being spread out so much more widely. It is not

just in the few very sophisticated academic centers. So I would like to keep in mind what happens out there in the community where you do not have the sophisticated IRB operations. And it seems to me that these people need as much guidance as they can possibly be given and that is why I would -- again I would favor strong, strong language.

I would favor -- I guess what I would like to see is as much guidance, concrete guidance as possible given to the IRBs along with a compulsion that these are issues that they really need to think about very carefully.

PROFESSOR CHARO: Marjorie?

DR. SPEERS: In writing this recommendation we may have had a less lofty goal in mind so let me just at least share what that was.

When you look at some of the federal statutes for protecting confidentiality such as the one education has, justice or CDC, those certificates of confidentiality not only protect against compulsory disclosures but they also prevent the researcher from disclosing the data so that a researcher, an investigator, cannot just decide to disclose data to another researcher, for example.

The certificates of confidentiality only protect against compulsory disclosures. They do not say anything about the researcher if the researcher decides to disclose.

So that part of what we were trying to do here was simply to set the same standard as the federal statutes have that

the researcher, the investigator is -- would be prohibited from voluntary disclosures without the participants' informed consent as well as compulsory disclosures.

PROFESSOR CHARO: You do realize, Marjorie, though that that would mean that researchers would be more constrained than other professionals. For example, lawyers and physicians' codes of ethics specifically contemplate breaches of confidentiality when it is needed to prevent an imminent harm to others.

So this is a very important -- this would be a standard for researchers that is different from that of other professionals. Now that may be justified because of the relationship they have with participants but I am not sure I feel like we have actually debated what that code of ethics for researchers ought to be before having decided that there ought to be some enactment that would concretize it.

I am sorry, Eric. You had said you wanted to -- and then, Tom, I think you --

DR. MESLIN: Just as a matter of historical referent when you discussed the HBM report you agreed to a recommendation that put a toe in the water of this topic. The recommendation was concerned about existing discussions about privacy of medical records issues and how that was affecting current discussion about research use of those records.

And you recommended -- it was Recommendation 23 of the HBM report -- that when drafting medical records privacy laws state and federal legislators should seek to harmonize rules

governing both types of research and such legislation, while seeking to protect patient confidentiality and autonomy, should also ensure that appropriate access for legitimate research purposes is maintained.

I take it that you are expressing a principle that captured some of the kind of issues that are going on here. Nuanced or not.

I think we are assuming that that principle still stands and NBAC did not take a position about privacy legislation that was being drafted at the time the HBM report was being written but it was foreshadowing the possibility that in this report it might want to -- if the commission might want to say something more specific if opportunity arose.

Well, the opportunity has arisen for you and I think that you may have a couple of complimentary options. One is to state even more clearly what you meant by Recommendation 23 getting rid of the medical records privacy issue and focusing only on research issues as they relate to privacy and confidentiality. We have done this in all of the chapters. We have tried to say as noted in previous reports this is what we said.

The second thing that you can do and you may not be able to resolve it right at this table, there are five commissioners who are not at the table who may have views on this, including the chair, and I do not know what Harold's views are about this proposed recommendation. We have not spoken to him about this.

But you could do both what Bernie wants and what Tom

wants in that the description of the principle, which is what Bernie was describing, can be far more exhaustively described for all the reasons that he mentioned and Trish mentioned about genetics research.

I do not see just as a matter of consistency with previous NBAC recommendations why a proposal regarding specific federal action at this time is inconsistent with or premature for all the reasons that Tom raised so I am just reminding you of what you have said before. I think that is one of my responsibilities and say that this is not -- you are not inventing this for the first time at this meeting. You did contemplate this problem a year ago.

PROFESSOR CHARO: Larry -- sorry. Tom and then Larry.

DR. MURRAY: Well, I am very grateful to Marjorie, Alta and Eric for enriching my understanding of what is at stake here in this recommendation.

And I now feel that certainly the fairly absolutist language in the second half of the recommendation is probably inappropriate because there may well be cases where you want to say to investigators that you ought to harmonize your reporting requirements there with your reporting requirements as a clinician, for example. So if you see child abuse it is -- but I still -- I guess, I would still like to see us make a strong recommendation that there be some clear public policy on this understanding that it may -- it is going to be something less than this -- the language will be less than the absolutistic language

because we are looking at several different -- at least two.

At least two. We are looking at protecting against third parties coming in and demanding it. We are looking at the moral obligations of investigators, people who are in possession of this information and what their obligations are to handle it.

PROFESSOR CHARO: Larry?

DR. MIIKE: Just a reaction to Eric's reminder about the HBM report. I do not think it is relevant to this discussion. That toe in the water was concerns over access to medical records information and other types of data which the privacy legislation threatened to cut off all together by going overboard in one direction.

And here we are talking about going in that same direction that the medical privacy act that we were worried about in the HBM report is going so it is not on point.

So I -- so basically what I am saying is that we are not inconsistent. As a matter of fact, we would be inconsistent if we push forward on this and push forward almost absolute confidentiality in the research setting because we would say, look, when you are talking about in the greater social context medical privacy please carve out an exception for researchers. But here now we are saying but in a research context we do not want any exceptions to anybody else on the outside.

My basic point is I agree with what Bernie and others that have agreed with what he is saying, is that this too complex an issue for us to incidentally address in this report. I can

agree for us raising the issues about all the competing interests that arise in this area but I do not think that we can address it in the specific recommendation.

How we do it -- there have been several times that have come up now where we want to make some statements that are not really recommendations and I think we can do that and also improve the way we present these recommendations because this ought to go one, two, three, four, five, six, seven, eight, but they are not clustered. They are on informed consent issues. They are on confidentiality issues.

And in the introduction to these recommendations can be a paragraph or so which can raise these kinds of things that, you know, we want to spotlight but not be in our recommendation.

PROFESSOR CHARO: Bette?

MS. KRAMER: I actually have a question that I would like to address to people who serve actively on IRBs and specifically to researchers themselves and that is would the existence of -- would the existence of stronger language around these issues be an aid in terms of the informed consent process?

PROFESSOR CHARO: In my experience it absolutely would be because there is a constant confusion as to what to tell people.

MS. KRAMER: Well, isn't that -- I mean, isn't that a good and substantial reason for requesting a clearer definition of privacy interests and confidentiality?

PROFESSOR CHARO: I think it is possible that, in fact,

Larry and Bernie and Tom's concerns can be somewhat addressed at the risk of loading yet another task on the central office, however renamed. But it strikes me first that in his discussion we have separated out the two components here. One is the researcher's own instincts at times to breach confidentiality for some purpose as distinctly different from the researchers trying to protect their data from an external body that wants to get a hold of it.

On the former what we lack is a developed researcher code of ethics. There is no such thing really and we have got a lot of active professional societies now that are working around the accreditation and certification process that are also well positioned to be thinking about that and, you know, if such a central office were finally created then they would be in a position to try to facilitate that kind of creation of a professional ethic which has always run for all professions along side rules and regulations and laws as one way in which there is a degree of self-governance.

On the resistance to third party and state agencies or district attorneys, et cetera, I am persuaded that the precisely correct approach has not been identified yet and that it may not necessarily be through federal legislation but I do sense around the table a notion that this is important if only because we both think that confidentiality should be promoted whenever possible and whenever it is not inconsistent with a really overriding public need.

And, second, that we recognize that there may be over riding public need and we cannot detail them right now. So I wonder if it is possible to call for a federal policy that strongly protects confidentiality while recognizing these over riding concerns and seeks ways to create a policy that is understandable and, hopefully, uniform across the nation.

MS. KRAMER: Can I speak once more? I am sitting here and I am trying -- I am thinking to myself, now, suppose -- suppose I was solicited to participate in a research project on mental issues, genetics, genetic testing, identification of genetic variations that would indicate a -- the possibility of some kind of mental issues within the family, et cetera. That sort of thing.

And on the one hand I may be very tempted to do it. You know, I may feel as though I want to do it but I can be absolutely certain that one of the questions I would really want answered for me is what is going to happen to this information and how protected is it going to be. How -- you know, how apt is it to get out and get into the hands that I might not want it to be in, et cetera? I think that it would be awfully important as we go forward with these genetic considerations.

PROFESSOR CHARO: Eric?

DR. CASSELL: Well, all of this, it seems to me, we cannot leave a hole in the recommendations because the hole is apparent that there is a hole in there. And on the other hand, the more concrete we make the recommendation the more trouble we

get into on the other side.

So I think that your recommendation looking for guidance and so -- that is -- we should put that the way you put it out. That is just fine. That way we have not left a gap. We have made it clear that this is important and that it has to be -- and that punting is not bad in this instance.

PROFESSOR CHARO: Maybe it makes sense to move on as we attempt to get close to the end of the recommendations before lunch. This is obviously one we are going to be coming back to I suspect on e-mail and then again. I think this is also where the public comment period might turn out to be tremendously helpful with lots of good ideas flowing in and stories that illuminate these problems that will give us more to work with and maybe the perfect answer will come to us later as a result of that.

Trish, I am sorry.

PROFESSOR BACKLAR: I am sorry. Just in relationship to this, in Oregon, you know, they have passed a privacy -- genetic privacy legislation and we are -- I am on the committee that is revising that. The people are very, very, very concerned about their keeping their privacy and breaching of confidentiality. I agree with Tom that it is terribly important.

PROFESSOR CHARO: It is not. We are not questioning the hot button issues of the day.

PROFESSOR BACKLAR: And we cannot really leave it. One of the things that I think would be very helpful, Alta, also would be perhaps even to have another one of these little tables or

things to show things that may have to be breached. In other words, a little picture that shows what should be kept, what should be -- what you cannot keep confidential because it harms other people or even the participants. That would be very helpful, I think, for people to visualize.

PROFESSOR CHARO: Okay. Recommendations 3.11 and 3.12 take us to the area of vulnerable populations. And 3.11 suggests a move away from the current way in which vulnerable populations are identified to one that is a little bit more reductionist and allows for more of a nuanced evaluation of the specific participants in relation to the specific protocol and the floor is open for people's reactions.

MR. OLDAKER: Are we on 3.11 and 3.12?

PROFESSOR CHARO: We might want to try to start with 3.11 because 3.12 goes then to very specific rules about decision making.

Bill?

MR. OLDAKER: I think I agree with 3.11. I would like us, if we could, to substitute a word for "taxonomy" so that those of us with less understanding --

DR. CASSELL: The non-zoological types, is that what you mean?

(Laughter.)

MR. OLDAKER: But other than that I think it is fine.

(Laughter.)

PROFESSOR CHARO: Other reactions?

Bette?

MS. KRAMER: I would particularly like to compliment those who are responsible for that, the language in that whole section, for the whole description of it. I thought that was just superbly done.

PROFESSOR CHARO: I agree. It was probably the most sensitive treatment of that topic I have seen to date.

DR. CASSELL: Would you accept classification, Bill?

MR. OLDAKER: Yes.

(Laughter.)

PROFESSOR CHARO: I will put my two cents in. The only thing I might add would be -- and not necessarily, I am not sure if it would go in the recommendation or ultimately in some scripted text but this taxonomic or classification style approach is going to be a little harder for IRBs in the beginning. Right now it is very simple. You have got somebody who is a prisoner and you have got a set of rules and you always follow those rules and it does not matter what the research is about. It could be about whether people have blue eyes or green eyes but this is the way you follow the rules.

They are going to have to do a lot more thinking for themselves right now and somewhere along the way some guidance about how you would kind of tick off the number of ways in which this population is vulnerable in this particular setting and the kinds of tricks that -- you know, the tools that you would use in your tool box, and our reaction to that would be helpful. I

really suspect that that is probably yet another politburo assignment but I do think that it is inappropriate to make the decision making process this much more complex without accompanying it with some help.

3.12? Hands are jumping. Jim and Bernie? Oh, I am sorry. Bernie?

DR. LO: A comment on accompanying text. I would like to see us give some examples of contemporary research that misses the boat on vulnerability. We give sort of broad categories of what we mean under each type of vulnerability but, you know, I think one of the concerns I had reading through this is that we all know there is a big problem and some of our readers will know that. There are other people who will say, you know, we are just doing fine. We are cranking out all this research, funding is up, you know, somatic cell gene -- you know, germ line gene therapy is right around the corner, you know. What is the problem?

So I think it would be nice to give some contemporary examples of disturbing studies on the basis of vulnerability that might have come out differently had they used this vulnerable scheme rather than the prisoners, children and the fetuses scheme.

PROFESSOR CHARO: Okay. 3.12? Professor Childress and then Arturo?

DR. CHILDRESS: I am particularly concerned about the second sentence, which seems to me to be at odds with what we recommended in the capacity report. And because, for instance, we may well have an advanced directive, Trish's favorite category,

plus a legally authorized representative, and for greater than minimal risk research that could be conducted under some circumstances. So at least we need some consistency there.

And I was not here for the discussion of nontherapeutic and therapeutic procedures I guess that took place. That may well have a bearing on how we go about revising this. But obviously part of the issue would be for some of the nontherapeutic procedures involved that may well be important as a diagnostic matter along with, I think, therapeutic procedures that are being provided but I will not say more since I do not know how that previous discussion --

PROFESSOR CHARO: Marjorie, can you clarify for me just -- I have read this sentence a little bit from Jim and I want to make sure I understand. With the exception of the advanced directives, which is omitted, I read the sentence as accurately reflecting the capacity report's recommendation, which was that a third party could not consent to greater than minimal risk research that no prospect of direct --

DR. CHILDRESS: In part, it is a matter of wording. The way it is stated here it does not say that.

PROFESSOR CHARO: Really? Okay.

DR. LO: Jim's right. It says "therapeutic" here.

PROFESSOR CHARO: But a risk associated with nontherapeutic procedures are greater than minimal risk, research should not be permitted.

DR. CHILDRESS: But we are going back to the earlier

part where we distinguish the therapeutic and nontherapeutic in terms of components and my contention would be that this as stated is inconsistent with what we said in the capacity report.

PROFESSOR CHARO: All right. Well, for sure, we want to make sure --

DR. CHILDRESS: Again, especially -- I mean, first of all, if the possibility of advanced directive plus legally authorized representative, that would permit the action here. So at least that would be modified in that way but I think it would have to be modified more than that but at least that --

PROFESSOR CHARO: We have to make sure that the language matches.

Arturo?

DR. BRITO: My comments are exactly the same. I had the same concerns and I interpreted it the same way.

PROFESSOR CHARO: Okay.

DR. BRITO: And I have my notes here that it is inconsistent with the capacity report.

PROFESSOR CHARO: Bernie?

DR. LO: This is one of the situations where as I try to think of the implications of what we are saying and the differences between the current regulations, I had some questions about the treatment of children.

PROFESSOR CHARO: Yes.

DR. LO: So, as we all know under -- the current federal regulations give very detailed guidance for research on children

and they have a tripartite distinction, not just therapeutic. We rejected that in the capacity report.

But what is now permitted under the current federal regs for children is research that does not offer the prospect of direct therapeutic benefit but has the potential for -- I do not know the exact words but it is gathering important information about the child's condition or the condition of children in general and there is a balancing of the benefits of that type of research for the underlying disorder versus the risks. And that you are allowed to have parents give permission for that kind of research.

That research would -- as I read our current 3.12 -- would no longer be permitted. The background is that, you know, we are beginning to understand that we just do not know a lot of fundamental information about children as a result. Children as a group are penalized by having a therapy driven by less than optimal -- by less than an optimal scientific base. It is not just the clinical trials have excluded children but we really do not know as much as we would like to about how children's pathophysiology differs.

So that whole discussion runs into what we are doing here. Now I personally favor the pediatric formulation and I would be very interested in having people like Duane Alexander from NICHD and eminent pediatric researchers tell us if that set of regulations work because we are tossing all that out now for a group of a subjects, namely children, for whom there has been a

lot of concern that they have been protected too much and as a result have suffered by having inadequate therapy and an inadequate understanding.

So I just think that I would like to sort of keep in mind that balance and think about how 3.12 would affect that.

PROFESSOR CHARO: Eric, and then Larry?

DR. CHILDRESS: Yes. I think we have to look at that also. I am not in favor of multiple levels of risk because it is just too complicated and there are always exceptions and so forth but we should remember that in this -- as written here, the fact that the children have parents does not show up. I mean, they are not exactly the same as a cognitively impaired adult with a surrogate. There is a long social history about surrogacy of parents and while it has excesses it has also got real reason.

So I am with Bernie. I think we have to make sure that we do not fall back on the previous children ones or on the other hand throw them all out.

PROFESSOR CHARO: Larry?

DR. MIIKE: I think we should greatly modify 3.12. It introduces the concept of minimal risk and I think that 3.12 should be rewritten along the discussions that we had earlier around the issue of minimal risk and vulnerability where we are now talking about vulnerable populations and so we concentrate on what we mean by minimal risk in vulnerable populations as separate from our previous recommendation on minimal risk rather than getting into the morass of starting to deal with some of these

things like noncognitive, et cetera, because we can leave that up to the implementing agency to revise according to our general directions.

Along that line, the last sentence of 3.12 more properly goes with the discussion in 3.11. It says "central office should also issue guidance describing safeguards for different types of vulnerability."

So the first recommendation on vulnerability should be the analytical approach instead of categorical approach, and revisions along that line. And the second is that in the vulnerable population what we mean by minimal risk is different from what we mean for the healthy normal -- other than the vulnerable population.

PROFESSOR CHARO: I have to say I am sympathetic with Larry's comment that we need to take into account the way we are talking about minimal risk now in the amended version. We need to be asking about research that is minimal risk to these particular people in this particular protocol versus minimal research that is not -- and I also share some of Bernie's concern about the way in which some of the protections that we are used to seeing are dropping out from the headline news version of a recommendation.

For example, the notion that if a population is vulnerable in the context of the particular protocol at issue that you would not use it unless you have to, which is a typical kind of protection that we have adopted across the board for these kinds of populations yet it no longer appears and maybe it would

reemerge in the guidance but I have always been very supportive of that one.

I differ with Bernie, however, on the issue about the children in research and I appreciate the point that parents have a different role than spouses or adult children or siblings in the protection of somebody who is unable to make decisions for himself or herself but we heard a lot during the years of the capacity report drafting about the difficulties in any kind of uniform implementation of the current children's regs because of the wide variation in the understanding of what is a minor increment over minimal risk, which would permit research to go forward still with parental authorization.

We did in the capacity report recognize this tension between including people for the benefit that it is higher class and protecting them from being drafted into research that poses more than a minimal risk to them. And we came up there with a mechanism by which we said, "Look, we will take it temporarily out of the hands of individual IRBs, have a central panel that looks at these things, and then can issue not only protocol by protocol but category by category decisions saying in this case it seems like the societal benefit is really important and the level of risk, although more than minimal, to this population is still within the tolerable range and now we will send it back to the IRBs for individualized implementation hereafter."

I want us to consider looking at the solution we adopted then and asking whether we still think it is a reasonable solution

to both protect subjects and obtain some uniform treatment of subjects and then have an escape hatch so that socially important research is not foregone.

But this is a problem and it is four minutes to 12:00 and what this does is it launches us on an entire discussion of the protection of children, which could be a report in itself.

Bette?

MS. KRAMER: But also before we leave this discussion I would like -- there is a sentence in the recommendation that I cannot figure out and it is a sentence that is at the top of the last page that begins "for other types of vulnerability." Can somebody clarify for me what that is talking about?

PROFESSOR CHARO: I understood it to be where the nature of the vulnerability does not involve your ability to make decisions but it is something else. For example, people who are let's say economical circumstances might be considered vulnerable for the purpose of protocols that have financial inducements.

DR. SPEERS: Bette might be asking a very basic question about how minimal risk has been used in the past. It has been used in two ways. One we talked about earlier today as a sorting mechanism as to what gets full board review and what does not. The other way that it has been used is to limit exposure, which is a way that it is currently used, if you will, in the children's regulations and to some degree in the prisoner regulations, which is if things are -- if a study is more than minimal risk, you know, then we do not permit that type of research.

MS. KRAMER: So here it is talking about limiting exposure, research exposure, as in Alta's just previous remarks. I think it is a very confusing sentence in and of itself right in the recommendation.

DR. SPEERS: Okay.

PROFESSOR CHARO: Arturo?

DR. BRITO: Marjorie, I have two questions. One is more just the vocabulary used here. In the second sentence where you involve cognitive incapacity, it is a little bit confusing because if you read the text before you describe the different -- the potential participants may be cognitively vulnerable because of lack of capacity. They cannot exercise their capacity effectively, et cetera, et cetera. So that is a little confusing but I still worry about that sentence for the same reasons that Jim iterated before.

One thought I had is this recommendation -- if you go back to the component based protocol, you know, however we revise it, how would this fit into that scheme?

It is right before lunch and I know this is not, you know, a simple answer but I am just thinking. I am trying to think how would that fit into the scheme and is this something that we need to think about.

DR. SPEERS: Do you want the quick answer?

DR. BRITO: If you have a quick answer --

PROFESSOR CHARO: If you have a quick answer, by all means.

DR. SPEERS: I do not have a satisfactory -- do we have -- okay.

PROFESSOR CHARO: Okay. Please. Give the unsatisfactory quick answer.

DR. SPEERS: The very quick answer is that what we are -- I will tell you what the thinking is even if the recommendation did not say this clearly.

The thinking is that for most types of vulnerability we are not recommending here to limit the exposure of research to those individuals. That is to say that for most vulnerabilities individuals could participate in research.

The exception to that or what we want to think about is when there is a cognitive vulnerability.

Now taking that thinking and going back to the component analysis, the same type of analysis, therefore, would be done in studies involving people who have some type of vulnerability. We still do the same kind of component analysis.

The difference is -- and based on the discussion that we had earlier this morning where on both sides, if you will, of that diagram, one would take into account the risks and potential benefits, that same kind of analysis is done when you are working with vulnerable populations.

The issue is whether for individuals who have a cognitive vulnerability, whether there are certain types of research that would not be permitted, in which case you would not do the analysis.

DR. BRITO: So you would not go through the whole analysis?

DR. SPEERS: And maybe just to go full circle but based on what I have heard here today, if we go back and look at some of the arguments and recommendations that you made particularly in the capacity report we would want to revise this.

PROFESSOR CHARO: When it does get revised it may be that it will be helpful to try to be less concise and instead write it out in a more leisurely way and say for these kinds of vulnerabilities this level of risk is or is not acceptable, these kinds of people cannot make decisions, et cetera. It may make it easier to go through and know exactly what we are debating.

Well, although we are two minutes after 12:00, I have a feeling that we will probably dispose of 3.13 pretty quickly unless I have missed something big there.

Trish?

PROFESSOR BACKLAR: Back to page 51. I am concerned that there is already a program of research on research and I am -- and some of that is quite done, you know, by Paul Appelbaum, for instance. I would be concerned back in the text that you would give some recognition to that research and not ignore it.

PROFESSOR CHARO: Okay. Diane?

DR. SCOTT-JONES: Have we finished with vulnerability? Are we going to be returning to that at any point?

PROFESSOR CHARO: Oh. We will be returning to it many times I am sure.

DR. SCOTT-JONES: No. I mean later this afternoon since you are wanting to break right now.

PROFESSOR CHARO: I am hoping we can break soon. I know that the staff is thinking already about redrafting it. So if there is something you would like to them incorporate in the redraft, please tell them.

DR. SCOTT-JONES: I just had a question for Marjorie. In reading through the way you have laid out vulnerability, I like a lot about it but I am just wondering whether it adequately represents children. You could put children in more than one of these components.

You could, I guess, put them under, you know, the section dealing with cognitive capacity or detrimental vulnerability or, you know, many of them could fit under there but they do not exclusively fit any of these categories. So their own uniqueness as children -- I am just wondering what you think about that. Is it adequately represented there?

And then I have another question about the taxonomy in general.

It seems that some of the vulnerabilities are due to conditions that reside in the person but at least one of them, which is socially devalued groups, that resides in the way others perceive them and the way others treat them and really has little to do with a characteristic that resides within the person so it is a different kind of thing.

I just would like to hear more of your thinking at some

point about this taxonomy of vulnerability and particularly how it serves children.

We can stop if you are ready to stop.

DR. SPEERS: Another quick answer.

PROFESSOR CHARO: Sure, please.

DR. SPEERS: Which is my sense is from this meeting that the way we have characterized vulnerability is something that, in general, you are comfortable with. So there are two ways for us to expand upon this. One is for us to talk about, as we had recognized, that individuals can have more than one vulnerability and so we need to do that.

The other thing that we want to add to this section is to add a table that actually looks at some of the groups now that are considered vulnerable and show how this new taxonomy or classification would apply. So I think that that can expand upon what we have here.

PROFESSOR CHARO: And certainly whether or not the vulnerability is something that is intrinsic to the person that is imposed by others would be relevant to the remedies that one might adopt for the vulnerability, right?

DR. SPEERS: Yes.

PROFESSOR CHARO: Tom?

DR. MURRAY: About 3.13. The recommendation language is fine for me. The description leading up to it seems to focus only on empirical research. I wondered if that was a conscious decision by the commission to exclude other forms of research and

to -- for example, conceptual clarification, ethical implications -- or whether we ought to in the description --

DR. SPEERS: It was not intentional on our part and I do think it ought to be expanded myself.

PROFESSOR CHARO: With that I am going to suggest that we break now.

You will notice that there is an hour-and-a-half, now an hour-and-24 minutes scheduled for lunch. That is because we never get back on time when there is an hour. But now we have enough time to get back on time so we are going to begin the public comment period at exactly 1:30.

(Whereupon, at 12:07 p.m., a luncheon recess was taken.)

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

PUBLIC COMMENT

PROFESSOR CHARO: We are going to begin and we have three people who have requested some time before the commission. Let me emphasize that those who have not requested time already are welcome to put in a request now.

We ask each person to speak just once and for five minutes, and we welcome written submissions that go far beyond what a five minute presentation would permit.

The first member of the public who has asked to speak is Howard Mann.

Thank you. Welcome.

HOWARD MANN

DR. MANN: Good afternoon. I am Dr. Howard Mann. I am chairman of the IRB at Intermountain Health Care in Salt Lake City.

I would like to address one issue and that is Recommendation 3.3, which addresses the issue of minimal risk.

It appears that the commission is embracing the notion or entertaining the notion of so-called absolute standard for minimal risk and I think this is a difficult issue and I would urge you to consider the possibility of what I might describe as contextual risk.

Let me give you a scenario. Let's say we have -- and this is particularly applicable to the notion of minimal risk in the context of a request for the waiver of a requirement for

informed consent. The scenario is a critically ill patient who is in acute respiratory failure because of the adult respiratory distress syndrome. The patient is on a ventilator. Being critical ill, this patient is unable to give informed consent.

I would just allude momentarily to the notion of getting consent from a legally authorized representative. That in and of itself, as you well know, is a very difficult and vexing issue because of the lack of definitions for the same in state law.

But, for example, if the researcher entertains the notion of applying for a waiver of the requirement for an informed consent, this might be the scenario and I think it is quite plausible. It is a randomized Phase III trial in which both arms of the trial involve a treatment that may be an indeed are applied to patients by physicians outside of the context of the trial. And the treatment is just an evaluation of two modes of ventilator therapy.

In that particular scenario we have clinical equipoise, that is by definition almost minimal risk then pertains. No nontherapeutic interventions are planned. None are really needed to evaluate the therapy. So again in that particular context of this particular trial where clinical equipoise exists, I think that a plausible claim of minimal risk can be made.

In fact, there are some that would make another plausible claim that in this particular context just by virtue of being a research participant one is exposed to perhaps diminished risk deriving from the quality and quantity of expertise,

monitoring that is usually associated with that kind of trial in that kind of setting.

So that I perceive a problem if an IRB was faced with that kind of decision and the only criterion that one could use is the absolute standard. I think that a calibrated contextual standard for minimal risk taking into account the actual proposed trial would be something that is worth considering and I do not think that it would necessarily "allow" ill participants to be exposed to greater risks than healthy ones without providing them with offsetting potential benefits since risks in nontherapeutic components are justified by potential knowledge gains, not by potential benefits to participants. That might sometimes be the case but not necessarily the case.

Thank you.

PROFESSOR CHARO: Members of the commission? Eric?

DR. CASSELL: Well, I just want to clarify. Assuming the trial that you have, one of the functions of minimal risk is that -- where minimal risk is present, the protocol might be subject to administrative review and move on but nobody would ever subject this protocol to just administrative review, would they?

DR. MANN: No.

DR. CASSELL: Because there are too many issues. Next, the issue of risk in and of itself. There is no standard of risk that you could think of that would be -- that you could universalize. I mean, you could not even use context here, could you?

You have a program in which two groups of patients are being subjected to different interventions and the issues will be -- will revolve around whether harm is being done to them. Whether, in fact, they are being protected. Harm is being done, benefit could come out of it, but the issue of minimal risk will not come up, will it?

The issue of a level of risk per se will not come up there. In such a risky world already, how will the issue of risk come up?

DR. MANN: The issue of minimal risk may come up in this particular context because these patients are unable to give consent and the investigators wish to conduct the trial specifically after having requested and received a waiver of the requirement for informed consent.

This kind of trial is commonly done in critically ill patients.

DR. CASSELL: I may be not getting it but I think that this is something where the IRB would have to review the protocol.

DR. MANN: Yes.

DR. CASSELL: Yes. So even the waiver issue. It is a special kind of trial. There is no way you could set a standard apart from that. It is a special kind of a trial that would have to be dealt with. The waiver of consent is because there is no possibility. There are no surrogates either. Nothing?

DR. MANN: Correct.

DR. CASSELL: There are no surrogates either. They

might --

DR. MANN: There may be surrogates but they may not be legally authorized representatives so in this particular situation the investigator has requested a formal waiver of the requirement for informed consent. There may, indeed, be surrogates but by operation of state law they may not be legally authorized representatives.

PROFESSOR CHARO: Dr. Mann, if this were to occur in a nonresearch context and the physicians at your institution simply wanted to begin one or another of these interventions as a form of therapeutic care. Wouldn't they ordinarily have to get permission from somebody?

DR. MANN: They would get permission. They would get permission from a surrogate but in this particular context when you get permission from a surrogate under the context of state law you will be getting permission for health are and not research.

PROFESSOR CHARO: And so your concerns would be adequately satisfied then if, as happened in the report we did on research with people with cognitive impairments, one were to treat a situation like this where the research intervention is one that may be therapeutic as equivalent to a situation in which it was clinical care and allow surrogates to offer permission?

DR. MANN: That is true to the extent that if state law, for example, was amended legislatively to promote surrogates to be a legally authorized representative for research in this particular context that would, in fact, address that issue and --

PROFESSOR CHARO: Are you understanding what --

DR. MANN: -- what already does happen.

PROFESSOR CHARO: Are you using the word "legally authorized representative" to mean somebody like a court appointed guardian? Because our understanding of the term is that it varies from state to state and does not require formal court appointment, and can operate automatically in terms of next of kin in many situations but that it is a state by state matter.

DR. MANN: My understanding is that most states do not have statutes that address the notion of a legally authorized representative for research purposes. That presumably would have to be a customized court appointed guardian for that particular purpose. But the problem right now as I understand it is the very dearth of statutory provisions for a legally authorized representative for research.

PROFESSOR CHARO: Trish?

PROFESSOR BACKLAR: I have a candy in my mouth. It is difficult to speak but an institution, as we wrote about this in our capacity report, an institution could put in some standards of which they would operate. So, for example, an institution in your state could decide that they wanted to be able to have a legally authorized representative and they could write their own rules that would be followed in their institution. And, in fact, an example, of course, is Oregon Health Sciences where we use the term not legally authorized representative because we felt people would muddle that up and think that it had to be somebody who was

legally appointed like a guardian. We termed this person a research authorized representative.

DR. MANN: I am aware that some institutions have so designated individuals. However, it is also my contention that current federal regulations, that is regulations that are promulgated by the FDA and the Office for Human Research Protections through the Common Rule do not permit an institution to designate a legally authorized representative but specifically defer to state law in that regard.

So while institutions may do that and perhaps have done that, I do not believe that is sanctioned by the current regulations at all.

PROFESSOR CHARO: Other questions or comments?

DR. MIIKE: Just a clarification. You talk about state law and legally authorized representative. Are you saying that -- I am not sure what the default position is. Is it that if the state has a definition of legally authorized representative and it says what is allowed, then everything else is not allowed? Or is -- do you see what I mean? Or is it when a state establishes a definition? Is it prohibitory or what? I am confused by your statements about what is allowed and not allowed by states with a legally authorized representative used in the statutory term.

DR. MANN: My interpretation is that if a particular state does have a law that defines a legally authorized representative for research purposes then in that state that law would apply but the problem arises in the absence of any law that

addresses the notion of a legally authorized representative for research.

In that particular situation individual investigators, clinicians, are left with a vacuum. They do not know how to make the decision. Up until this point in time it is clear that they have used --

DR. MIIKE: That is what I am asking you in a sense that if the law is silent, I do not understand -- and the lawyers in the group have to explain this to me as well as you -- I do not understand why you might say that, well, the guardian can make a decision for health care but it cannot make a decision for research. I do not see that as within the purview if something is silent on it.

DR. MANN: However, the problem arises because if you read the applicable federal regulations the federal regulations when providing guidance in this area specifically say that state law to the effect that it authorizes individuals to be a legally authorized representative for health care decisions are not thus authorized to make decisions with respect to research participation.

So given that those regulations exist, the fact that some states do have a law permitting individuals to make health care decisions, when one reads the regulations, one says, well, given what the regulations say, in this particular situation I cannot use that. I cannot have those people make research decisions.

PROFESSOR CHARO: We probably need to move on to the next person who is waiting.

DR. MANN: Thank you.

PROFESSOR CHARO: Larry, I would say that the lack of clarify is the problem. It is like a game of chicken. There really is no reason why they cannot go ahead and get permission from the next of kin. It is possible that the institutions are nervous that in one case out of however many the participant in the research will be unhappy this and will find a reason to complain legally about it and then there is some uncertainty about the outcome. That is what is going on here. Not that there is an actual prohibition but just uncertainty.

Thank you very much for pointing something out that is very important from the trenches.

The next person who has asked to speak is Colin Thomson. Welcome.

COLIN THOMSON

DR. THOMSON: Thank you.

Let me say that it is a privilege to be offered the right of an American citizen to appear at your public meetings and I do so as a member and the deputy chair of the Australian Health Ethics Committee, which is our National Bioethics body, and thank you for the opportunity for being here.

I know that my colleagues would join me in complimenting the work of the NBAC over the last -- over this -- its present life. Certainly we have gained enormously from your work on human

cloning and the report in the advice that we had to give our minister in 1998. I think we expect to gain equally from your reports on international research and the one that you are working on now because one of the priorities for the Australian Health Ethics Committee, or AHEC as we tend to call it, over the next three years is the support of our IRBs that we call human research ethics committees or HRECs.

And that is because a year ago Australian -- the AHEC produced a national statement on human research ethics and a national statement on ethical conduct in research involving humans. And so quite a lot of the discussion this morning has been something of deja vu for me, although at a level that is different. And I want to draw on -- I want to make a couple of observations about differences in our two systems and then make a comment, which I hope is more than just an ambassadorial one.

The two differences are we do not have 45 CFR 46. We may be happy about that. And we do not have OHRP either. It occurs to me listening to you this morning that the presence of the regulation means that a lot of the work that you do, the discussions at this meeting have been focused on your recommendations. AHEC, by contrast, in the absence of there being some regulatory structure to which it speaks, spends as much time on each page of this document -- I have a couple of copies which I am happy to leave here -- as you do on each recommendation. So that is a 62 page document. We spent four years doing that. Maybe that is -- that is no comment on quality. Just on process.

The absence of OHRP in Australia means that the Australian Health Ethics Committee does both in the sense that it has got to grapple with the conceptual and theoretical issues that you are grappling with now and as well the methodological and procedural issues which OHRP, as I understand, plans to do.

I think that gives you the wonderful privilege and freedom of dealing as you have -- I have not had the pleasure of reading this draft report but I will. I have read most of the international one -- of dealing with these conceptual and theoretical issues, which I agree absolutely are of great importance.

My comment is this: In our work we have realized that HREC members need two things, I think. They need guidance. They need to be given guidance on what are relevant considerations for the decisions they have to make. And they need what I would call enlightenment or understanding. They need to be taken a little deeper to understand what the concepts mean that we recommend they take into account when they are reaching decisions.

Whatever is the outcome of your recommendations to the central office, whoever that might come to be called, I would urge you to bear in mind that enduring audience of IRB members, they need the enlightenment that you can give them, and they need it on my reading of the -- several reports of the IRB system in this country over the last few years -- they need it perhaps desperately. I do not suggest that Australian HREC members need it any less.

But if that is an important audience, and I urge you to consider that it is an important audience, then in the way that you complete this report, particularly this one, that that audience be foremost in your minds as an important audience to whom to speak usefully and effectively so that their -- the quality of their work will be enhanced by what you do.

Thank you for the opportunity of being here. I will enjoy the rest of the time.

PROFESSOR CHARO: Thank you very much for your comments. They are very valuable.

Would any members of the commission like to extend the discussion?

DR. CASSELL: That ought to take us another two years.

(Laughter.)

DR. MURRAY: Colin, may I ask what your committee is currently working on in terms of its own primary reports?

DR. THOMSON: The agenda for -- see, we work differently. Unlike NBAC, we do not get the job of doing reports. We either do guidelines, which is what the human research ethics ones are, and we are required statutorily to do that, to provide ethical guidelines on medical research. We actually wrote them to cover all kinds of research and not merely medical.

It is interesting that for somewhat Byzantine political reasons the statute says that those guidelines must be issued in precisely the form that they are developed by the AHEC and cannot be amended by anybody. They can be rejected. So we work on

guidelines or we work on -- that is basically the kind of work we do.

The agenda over the next three years is the following: Support for human research ethics committees. And that will involve training, some approach to training, some consideration of accreditation. I think that is looming on our agenda. It has not been there. We have a voluntary system of 215 committees around the country who report statistically to the AHEC every year but not beyond that.

There is a joint reference to the Australian Health Ethics Committee and the Australian Law Reform Commission on the protection of genetic information in relation to life insurance. That will not come as a surprise to anyone around this table. What surprises us is that the time line is very relaxed but that has more to do with the workload of the other commission than with ours.

We will be working jointly with another standing committee of the National Agency on Diagnostic Guidelines for persistent vegetative state. We understand that there are not any and a certain judge in one of the Australian states was astounded that there were not and so we have been asked to look at that.

The extension of the human research ethics guidelines or the revision of some interim guidelines involving health research with indigenous Australians is the other major item. That may not sound like a major item to people around this table but politically the negotiations with the indigenous population in

Australia have become extremely complicated and that will be quite a demanding task to do.

Our hope is that by the end of the training we will be at a point where the national statement will be -- will have received some feedback, whether critical or otherwise. it does not really matter. And I personally would like to see it grow to include material specifically on anthropological research and social science research so that it is a much more inclusive and comprehensive document than it presently is.

PROFESSOR CHARO: Dr. Thomson -- I am sorry. Bette?

MS. KRAMER: I am curious. Who charters your commission?

DR. THOMSON: There is a statute. The National Health and Medical Research Council Act, which is a council comprised of about 35 people that are ministerially appointed. The Australian Health Ethics Committee is a standing committee of that council and it is appointed by the Federal Minister for Health. There is a set of 15 designated types of people. I am the person who has expertise in law and there is another bunch of other people. The minister must consider recommendations made to him by peak bodies in relevant areas before he makes a decision, he or she makes a decision on whom to appoint.

Beyond that its mission and charter is very general. To advise the Australian government and the Australian community on ethical matters in health. One specific responsibility was guidelines on -- ethical guidelines on medical research.

So it will have matters referred to it. Human cloning was one. Genetic information protection is another. And most of its work comes through matters being referred from the federal or the state level.

It has not in my knowledge of it in the last five years generated much of its own agenda.

PROFESSOR CHARO: Professor Thomson, we have had the pleasure of hearing from Donald Chalmers on a couple of occasions so we are not unfamiliar with your work but, I think I have forgotten if it is in your document, how the problem of confidentiality is being approached. And I know that you are here this morning. I would be interested in your reactions to the discussion about the creation of a policy governing confidentiality and appropriate breaches and such.

DR. THOMSON: To my knowledge there is not anything clearer or more consistent than what I heard around this table. We have exactly the same problems and exactly the same complaints from particularly social science researchers who feel that their records are vulnerable in ways that make it very difficult for them to encourage confidence in the participants when they seek to be involved.

There is a lot of statutory rethinking of privacy regulation in Australia. There are laws at both federal and state levels and there is an intention to drive the federal privacy regulation into the private sector. So far it has been confined to commonwealth or federal level agencies. That is being done by

setting up a kind of default guideline system that industries or industry groups like universities can set up their own guidelines, have them approved by the privacy commission at a federal level, and then they will be the de facto regulation. If an industry does not then the default code becomes its guidelines.

The sanctions for that -- and this may get some way of the way down the track but I do not think it is going to really resolve it, although because it is a complaint driven process -- protection of privacy is driven by people complaining that their privacy is being in some way infringed, there is a complaint resolution process. The aim being to resolve the problem.

If it happens that -- so universities adopt a privacy code approved by the commissioner and research participants are unhappy about the way their information is used, that complaint process might generate exactly the kind of national level thinking that you are seeking to have happen here but we are not -- I cannot say we are further ahead than you are regrettably.

PROFESSOR CHARO: Okay. Thank you. Any other questions?

DR. THOMSON: Thank you.

PROFESSOR CHARO: Thank you very much.

Kateri Harnetiaux?

KATERI HARNETIAUX

MS. HARNETIAUX: Good afternoon. My name is Kateri Harnetiaux and I just have two very brief comments and I am very happy that I saw that you were having a public meeting and thank

you for making this -- I mean, I am sure you had to because of being the commission but I am very happy to be here.

I only had two brief comments on the recommendations and one was what the name change could be for "central office." I wonder, Dr. Cassell, if you could mention what you had in your mind again?

DR. CASSELL: Well, I was trying to use a descriptive name. The office responsible for protection of human participants in research.

MS. HARNETIAUX: And I just really liked the shorter version offered of office of bioethics but I just thought I would suggest to make it real short.

(Laughter.)

MS. HARNETIAUX: And then I wanted to ask if you would consider removing the word "should" from each of your recommendations. And I do not know how important you think that word is but I think it should be a declarative statement since it is already identified as a recommendation. You know, "the office should issue regulations." I mean, I wonder if by making it sound more declarative it might send the reader back to the text itself to understand why you believe this as a recommendation they should apply.

PROFESSOR CHARO: Thank you.

MS. HARNETIAUX: Thank you.

PROFESSOR CHARO: Comments? All right.

Is there anybody else who suddenly got inspired to make

a comment?

Okay.

Well, it is 2:00 o'clock and miraculously we got sort of through Chapter 3 with some areas that are obviously going to be reworked.

And according to the Pig Latin version of our version of our agenda we now move to Chapter 2, right, going backwards.

So I want to direct everybody's attention to the first page of the handout as we embark on the question of the system.

Larry, I am going to count on you perhaps to get us started because you had indicated earlier today that you had some sweeping or over arching comments or concerns about the structure. It seems like as good a place as any to get started and then we will go through it recommendation by recommendation.

DISCUSSION: CHAPTER 2

DR. MIIKE: Well, my primary concern about the structure of the central office, it has been given not only establishment of regulations and interpretation and rule making and education, monitoring, enforcement and accountability, and I do not see how it can possibly do all of those things in a satisfactory manner. I have already mentioned to Marjorie that there is sort of a dilemma, though, because if we are going to extend --

DR. CASSELL: Larry, do you want to talk louder?

DR. MIIKE: If we are going to recommend extending the regs to all research regardless of funding source, which I support, it does cause a problem about how one implements and

enforces this.

If it were simply still within the federal system it would be a fairly simple matter to delegate much of the monitoring and accountability leg work to the sponsoring agencies with the central office or whatever we are going to call it more or less having oversight over those activities.

So I do not know how to deal with this because I think what we are going to end up doing if we go along on this particular course is an agency that is not only all powerful but is not going to be able to do all the things that we ask it to do so that is my main concern about the central office. Of course, we have left off -- I suppose even though we do not state it, what we are saying is that it should really be not attached to any particular department. I think that is clear even though we do not specifically state that.

But my main concern about the office is the scope of its powers in relationship to what I know its resources are going to be.

And then the other main issue I have with the recommendations in here is I see -- and this is an issue we discussed in the Human Biological Materials Report, which is including relatives of people in the definition of human subjects research and I just see that as a not implementable system when you consider what is required once you start saying that relatives are human subjects.

PROFESSOR CHARO: Certainly the latter we will get to

because it is very specific to one of the recommendations. In a sense your first comment kind of takes us directly to Recommendation 2.2. Let me try something out with your permission.

Recommendation 2.1, wording aside since it is -- you know, legislation is enacted by the congress but then signed by the President so we need to just correct the wording a little bit -- is there any -- is there going to be any problem with the sentiment in 2.1 which reflects the sentiment of the resolution from May 1997?

If that is the case then let's take Larry's comments as a starting point for a discussion on 2.2 since it is the one that suggests the creation of an independent single federal office to lead and coordinate the oversight system.

One concern obviously is that we are tasking such an office with too many things. There are other concerns that might be imbedded in here as well.

Bill?

MR. OLDAKER: I have always believed that the regulation that currently exists, and I must say I am not as steeped as many of you are in this, on human subjects is far too dispersed and if there is going to be credibility in the system you are going to have to have much stronger regulation in a centralized form.

If we look at the regulatory system that the Federal Government has either for securities or banking, they have a centralized format which has given everyone confidence in those

systems, and I think that if -- you know, no one thinks about it a great deal but if you think about just the securities laws in the United States, people come to this country to invest money because they have confidence in the regulatory system.

I think without a centralized body it is going to be very difficult to have a system that everyone can have faith in and that basically cannot be fractured. You cannot do -- have private research done one way and university research done another way in my mind.

My opinion is that there has to be (1) a central regulatory authority that will set the standards and (2) there has to be a central regulatory authority that has the power to discipline people when they do not live up to the standards as set forth. Without that I do not think you will have great confidence in the country that this is being regulated efficiently.

PROFESSOR CHARO: Diane?

DR. SCOTT-JONES: When I read the recommendations for the central office it seemed that there are many reasons to go in this direction and I tried to think of what would be the downside of doing this. And I wondered whether this could result in an office that is remote and out of touch with people who are closer to the actual process of research and I was wondering what safeguards could one build into the description of it at this point that would prevent it from being a remote office that is not really actively involved in the activities that we want to happen.

PROFESSOR CHARO: Other comments?

Larry?

DR. MIIKE: I do not want to be misinterpreted in this or misunderstood in the sense that I support some kind of central function. What I am worried about is what that office is -- what responsibilities are loaded on that office. I think we need something like -- well, it is the most convenient way in which to make sure that human subjects research is overseen uniformly and not left up to individual agencies or leaving it voluntarily to the private sector.

So an office such as the one that Dr. Koski is heading now is what I had in mind. It is just that again I just keep on reiterating that. I just do not see it being able to perform all of these functions adequately.

PROFESSOR CHARO: Marjorie?

DR. SPEERS: Let me make one comment to address Larry's concern, which is a concern and one that we have thought about and tried to deal with slightly, and maybe we need to do more with it. And that is we were envisioning this office to be essentially -- I am going to say a coordinating office, that there would be a structure particularly in the federal side where there is the central office and then each of the federal departments and agencies would have offices as well to carry out the functions.

So we tried to talk a bit about that in this chapter of saying that the functions, not all -- carrying out the functions is not centralized per se, that there needs to be a structure to do that.

And what we have not thought through enough that we probably need to give more thought to is how that happens on the private side. It is clear to me how the current federal structure works but we, I think, need to give some thought to how that would work on the private side.

And the other thing that I want to say that I want to make clear, at least when we wrote this, it may not be clear, is we do not -- we did not envision the new Office for Human Research Protections, Dr. Koski's office, being the central office. We believe that HHS needs to have a central office, which it now does, but there -- we were thinking about another -- a truly central office for all of research, all Federal Government. So if that is not -- I just want to put that on the table in case that is not your sentiment.

PROFESSOR CHARO: Bill?

MR. OLDAKER: Marjorie, I got from reading this that -- maybe mistakenly, but in some ways the Office of Government Ethics, which basically deals with the various financial disclosures and other things in the government has been set up as a separate office and the various agencies have their own ethical regulations. And I kind of gleamed that we were talking about a system somewhat like that.

The distinction is the one you point out, is that 40 percent of the research now is done outside of the system and I think that will grow, and that is different than the Office of Government Ethics. But I think -- and what that means to me is

that that is not a bad model but the Office of Government Ethics also has a super structure that the FCC or the Department of Defense cannot have a lower standard than the Office of Government Ethics sets.

So it sets the baseline standard at the very least and the enforcement to a certain extent in the government is done through the individual agencies but the Office of Government Ethics also has responsibility.

I think that the difference here is that you will find an increasing workload going on outside in the private sector and you have to think about how that enforcement will occur.

PROFESSOR CHARO: Diane?

DR. SCOTT-JONES: I am wondering whether anyone has thought forward to details such as how many people, how much resources would be needed to carry out this function because, you know, in reading it, the text has the language that says this office would work not through direct interactions itself but through interacting with others who then interact with -- I would imagine -- universities or private research corporations and there is a phrase that says "results can be substantially increased with small increases in resources."

Is this envisioned to be a very small office with a small number of people and few resources?

DR. SPEERS: I think, in general, we were thinking of this office as being a smaller office rather than a larger office because it is based on -- built on the structure we have now where

we have federal departments that have designated staff or have designated offices and we would want those federal departments to augment their offices. So that we do not see this as a particularly large centralized office.

PROFESSOR CHARO: Let me just make sure that the commission has on the record agreed to certain things or at least to initiate a debate if they have not that are implicit in this.

Regardless of whether it turns out to be large or small, which may be an important part of being able to answer Larry's concerns or not, this recommendation assumes -- well, this recommendation calls for an independent office that stands outside the current department structures. The chapter recites what we have been hearing every since virtually our first meetings about the advantages and disadvantages of an office within an department that does a lot of research that is then somehow designated to be the lead office among all other cabinet level departments and such versus an independent agency.

Is the commission comfortable with the decision to recommend an independent agency with all of the strengths and weaknesses of that approach?

DR. SCOTT-JONES: Do you want a show of hands?

PROFESSOR CHARO: If somebody is not comfortable with this I assume that they will speak out and say let's talk about this further before we accept this portion of the recommendation.

It is not forever hold your peace but it is, you know, if you are going to make a fuss, do it now.

(Laughter.)

PROFESSOR CHARO: The second thing that is implicit in this, which is probably discussed somewhat less but has come up in some of the discussions with members and chairs of IRBs. It has to do with the combination of functions within this office. It includes functions that you would associate with education and the promotion of research and research ethics, and it also includes a disciplinary arm having to do with enforcement. We have seen in other contexts historically, as has been described in papers from other people, from some of our contractors, that at times this has become a difficult tension. The old Atomic Energy Commission was separated into the Department of Energy and the Nuclear Regulatory Commission in order to separate the nuclear energy promoting from nuclear energy disciplining arms.

From IRBs we have heard some concern about the ability to seek guidance on sticky problems from an office that has just on the other side of the wall somebody who is sitting there ready to begin enforcement actions.

This proposal for the moment combines those functions and assumes that some administrative mechanism would be worked out that would be adequate to give people the confidence to go ahead and use the office for advice and for prophylactic measures without fear and retribution.

Are we comfortable with that?

DR. BRITO: I am comfortable with the concept but it just seems that the goals are very lofty here and seem too

diffuse. And I suppose we are talking about Recommendation 2.3 really now, what we are doing here because it really encompasses all these sort of --

PROFESSOR CHARO: Yes, I suppose. I did not mean to slide into 2.3. That is my error.

DR. BRITO: But it is actually -- the issue I had here with the supporting -- the background information before the recommendations was that it was very hard to understand after reading it all what exactly the central office would be doing and it was not specific enough.

And in my ignorance about these kind of regulations and things like this I thought just what -- it just seems that you need to be very specific if you include all these components into what the central office is going to be doing and you be very specific about it.

You know, I was very confused about the -- this one sentence, particularly page 20, about "the central office should carry out its functions through others, where possible, as opposed to operating through direct interactions," and the language that went on to show support for that it became more and more unclear to me what exactly the central office is going to be doing.

So I am in support of the concept but I would just like to -- I think we need to be very specific about what it is exactly we are supporting about what the central office will be doing.

PROFESSOR CHARO: Larry and Diane?

DR. MIIKE: Let me back up a second by saying that when

I mentioned Koski's office, I meant that in the global sense that they were supposed to lead the federal effort. Of course, I agree that there should be a central office. So I think we all support some idea of an independent office within the Federal Government.

Then the issue becomes what do we mean by that office because of its functions. I think it can do rule making, policy guidance and educational activities. The monitoring, enforcement and accountability actions, it seems to me that the central -- this independent office can establish guidelines or rule making for which at least on the public side the sponsoring agencies are responsible for monitoring and accountability. And they can -- the penalties for noncompliance would be withdrawal of funds. You can also talk in terms of keying in the FDA regulatory process for approval of drugs in those sides.

On the private side it gets a little bit more difficult but we also talk in terms of -- in terms of monitoring -- even on the private side I would like the independent office to stick to this idea about rule making, policy guidance and education.

And we can, for example, just off the top of my head, one can talk about a -- we are moving to a certification system of IRBs so that, for example, research should be conducted only under the auspices of certified IRBs, et cetera. And I think that in the textual explanations we can say what the connection would be between the central office functions and activities outside both in the private and public sector.

So my short answer is I support the central function but

it is so dependent on what we give that office and I think rule making, policy guidance and education are big enough pieces for them to do without having to get into having a whole army of auditors, you know, just a lot of field workers having to go out and doing the leg work, which I think should be left to other mechanisms and other agencies.

PROFESSOR CHARO: Bill?

MR. OLDAKER: I agree with Larry, I think, in most part. I think the enforcement is going to -- if it ever works properly -- is going to work on the certification and the decertification of IRBs or individuals who have been certified in these roles.

I think that once that occurs there will be -- and the other thing is we have to make sure that there is something that gives at least adequate economic funding to IRBs, which they are not, and we will talk about that later I would think.

But to me if the -- this new body does not in the first order have some reviewing of whether an IRB is decertified or not, I think it actually should have at least appellate authority. You need some uniformity here so that all of the various organizations are treated in approximately the same way ultimately.

I think that I probably agree with you, Larry, if we basically allowed whenever we got to the enforcement, it be enforced by the agencies themselves with the ultimate appeal to the -- whatever this group is so that there could be some uniformity in place so that you do not have different decisions being made as how you handle things in the Department of Energy

or, you know, from one department to the other because if we have that kind of fracturing in the Federal Government fairly soon we do not really have a uniform system.

PROFESSOR CHARO: Diane, and then Bette?

DR. SCOTT-JONES: I am still thinking about how such an office would function and even if we removed some of the functions as Larry suggested, the monitoring, enforcement and accountability, we are still left with a great deal that the office would do, especially if it is to be a small office with few resources and it needs to exert influence over many departments and much of the private sector that is involved in research. It is not clear how exactly an agency can do that although I am in agreement with the goals of it.

Take education, for example. Much of the education that needs to occur is at the level of investigators and IRBs. How would this agency exert some influence over educational activities if it is to rely on filtering down the mandate for education through departments and so forth? It is just not clear how this is going to work from what you have laid out here. So I think my question is a practical one having to do with how this would actually work.

PROFESSOR CHARO: Bette?

MS. KRAMER: Yes. My question is a practical one, too, and it is addressed to Bill and to Larry. And that is if you were to leave it to the sponsoring agencies to do the monitoring and enforcement of their own research protocols then who would fulfill

that role for research in the private sector?

DR. MIIKE: I have an answer to that.

MS. KRAMER: Pardon.

DR. MIIKE: Go ahead.

PROFESSOR CHARO: Eric, will you yield to Larry?

DR. CASSELL: I will yield to Larry. I would like to hear what the answer is.

PROFESSOR CHARO: The gentleman from New York yields.

DR. MIIKE: Sure, briefly. First of all, we are recommending establishing by federal statute such an office with certain powers. And it would be delegated the rule making authority and policy guidance and education.

What it would then do in terms of the monitoring and accountability of individual agencies on the public side is that this office would set out guidelines for what must be followed. Okay. And what I am saying is that, for example, if NIH is funding certain amounts of research it makes more sense for me for them to see an accountable system where people are following the guidelines for human subjects research. And if they do not they have the power to take away the money or not. The central office sets the parameters by which the agencies do this function.

On the private side it gets a little bit more complicated but I think we would now have a federal statute that said that private research is subject to this and I would leave it to others to say what would be the penalties if they boldly decided not to face it but there are other ways of doing that

besides civil and monetary penalties.

One is that in order to conduct research you must do it under say a certified IRB and the -- what it means to be a certified IRB can be defined by guidelines or regulations put out by the central office. And then some other kinds of things is that when you come with a commercial product to the FDA one must show that you have met all of these types of requirements in order to be able to get your product to the marketplace.

It is not a perfect system but what is? I mean, the Securities and Exchange Commission more often than not says their penalty is, yes, I promise never to do that again. You know, that is the kind of thing. The FDC does the same thing.

So it is more the threat of what can be done rather than the actual actions a lot of times and that makes the system run.

These are just off the top of my head but it seems to me that what we do not want to get into is that what exactly are we talking about, about the specific relationships. We should define what the relationship should be and what the responsibility should be but the actual ways in which you implement those I think has to be left up in the air.

And if congress takes us seriously about establishing a central office, in that battle that will go on in passing or not passing the legislation these are the kinds of issues that are going to be hashed out and become much more concrete in the real world.

It is impossible for us to do it here.

PROFESSOR CHARO: Eric?

DR. CASSELL: Well, I thought Larry just made a good case for a central office actually. But I think the education question is one which points out the need. A body like this has not just got regulatory power. It has also got moral power. It sets a tone for things. It says this is what education will look like and, in fact, ultimately it does. It filters it down through different organizations and requests that they figure out what education should be. By the time it gets down to the bottom it is watered down in such a way that it matches every other educational effort. We have called again and again and again for education. It is part of the things we do and there is not too much evidence that it happens.

It takes a stronger power and I think that this office central with large powers could do that. I mean, it would not do it easily at best. We understand that.

PROFESSOR CHARO: Please?

DR. SPEERS: This is the only time I will make this comment where I am going to essentially apologize for the way we wrote the report, which is to say when we wrote Chapter 2, at this point we had not written 3 and 4, and we still, you know, have not written 5. So some of the things that we have now said in 4, I think, we can go back and tighten up things that are in Chapter 2.

For example, in Chapter 4 we have talked about education and monitoring so we can go back and beef up or provide some of the linkages in Chapter 2 that are not there. This is assuming

that your sentiments are favorable towards Chapter 4.

This is also points to the importance of the Chapter 5 piece that deals with the interconnections in the system and points out how different pieces are related to other pieces. We, for example, in Chapter 2 really tried to stay away from accrediting bodies and certifying bodies because you have not talked about that but once it is discussed then we can put some of those pieces in.

So I am acknowledging a weakness here in this chapter that I do think we will be able to work on after this meeting.

PROFESSOR CHARO: I had two comments I wanted to add to the discussion. First having to do with the one about enforcement. It may be the lawyer's training. I also find myself drawn to that topic but I found myself beginning to step back and ask why we want to have enforcement.

One possibility is because we want to be able to prevent actual injuries to human subjects but all the anecdotal evidence suggests that those are pretty rare. The enforcement actions that have been taken so far as we have noted here tended to be quite prophylactic. They were enforcement actions based on inappropriate procedures where the procedures are in place because the thinking is if you follow them you are probably not going to hurt too many people along the line.

So it could be that it is about preventing injury but it also could be that it is just about maintaining public trust and maintaining the ability to have people supportive of the research

endeavor as a whole. And if it is public trust that may suggest different kinds of remedies. Right?

It seems to me public trust would mean that you need a system that is easily accessed by members of the public who perceive themselves as having been wronged and that there has to be an easy way for them to have their complaints handled and some response given and a credible response involving some way that there is some real investigation of what happened, and that this process has to be transparent to the people who perceive themselves as injured or those that see themselves as champions of those who see themselves as injured so that you can maintain the trust.

It may be that having a central office that has the authority to enforce but is encouraged to delegate, wherever possible, which will be frequently quite possible throughout the Federal Government, may be possible throughout portions of the private sector where you have got large scale institutions like universities that are capable of creating an internal enforcement mechanism, they should be encouraged to do it but reserve the privilege and the obligation to directly handle enforcement for those entities that fall outside the boundaries of all those existing entities.

So in a sense you would have to give them the power, Larry, but you would encourage them not to feel like they have to use it all the time. Right?

So I am finding myself thinking maybe there is something

along those lines that would satisfy everybody's concerns here.

The second I just want to throw out, and then I will turn to Bill, is a power that seems to be left out that I would like to raise for discussion. And that has to do with the function of being essentially an appellate IRB.

It may be that it is implicit in the phrasing in Recommendation 2.3 about policy development and interpretation or, indeed, rule making, although that seems like a really formal way of going about it but over and over in our previous reports we have found that it would be helpful on occasion to have special regional or national bodies that are devoted to special circumstances that seem to arise infrequently at individual IRBs that would benefit from uniform treatment or where you would like to have a second set of eyes.

We very specifically called for the creation of such a panel in the capacity report and I did want to urge us to at least consider how this new central body would relate to that function.

Bill?

MR. OLDAKER: I agree with you about enforcement but most of the enforcement -- you are right -- that is done -- and Larry is correct also -- in the securities area and other areas is fairly prophylactic. I mean it is out there and it is done but people do not have confidence in the system.

My view here was if we looked at certification of IRBs and one of the main enforcement would be decertification of the

IRB you would put the pressure exactly where I think it should be with the IRB and its members to do the right thing.

Right now at least from what I have read in the newspapers and watched, you know, there have been -- people have gone in and audited and the university's whole program has been set aside for a period of time.

I think that this might be a -- would be a more reasonable punishment and it would deal with the people who are actually -- who actually should be making the decisions but then that -- the other side of it, I think, we have to deal with later is the adequate funding of the IRBs to make sure that they actually get the funding that would allow them to function in a proper way and to get the education and training.

Now I think when you do this basically how it is going to work is there will be a devolution to various licensing boards that will actually probably take it up in the first instance. I think that is probably a much more efficient way to do it but that is not discussed here.

PROFESSOR CHARO: Bette?

MS. KRAMER: I have recently had some interaction with VCUMCV, which you may recall was one of the institutions whose research was closed down by OHR -- well, the prior --

PROFESSOR CHARO: OPRR.

MS. KRAMER: -- OPRR. And let me tell you something, that power to close down, to, in essence, withdraw the certification of the IRB and to close down that research

establishment is nothing to be -- is nothing to be blown off easily. I mean that has caused major, major disruptions in that university and let me tell you it has brought about -- it has brought about revolutionary changes in the way they are doing everything and I would assume that that is probably par for the course when an institution gets closed down. I do not know. It is the only time -- the only experience that I have had with that. So that is a very powerful -- that is a very powerful enforcement tool.

I think that this whole subject that we are discussing now, as I mentioned to some of you at lunch, is -- it is interesting that this paper, this project is the one that we were challenged to do, that we were charged with the obligation to do in the enabling statute, and I believe it was the first charge and yet it has been the last one that we have put on the agenda.

And it is interesting because as we have gone along it is apparent to me that each one of the subjects that we have tackled has brought up areas and has made a strong point of changes that are really required in the system.

And as I think about what we are talking about here, this is probably the most far reaching, the most far reaching recommendations that we will have made in any of our reports because to say that the Federal Government should now supervise privately funded research, that is a huge step. That is a giant step. And to talk about revising the whole way in which everything is done is a giant step.

And I hope that we are going to -- that we are going to have really good introductory material to all of this and acknowledge the fact that we know that we are making these really far reaching -- far reaching suggestions and make a strong case as to why we really think these things are necessary citing all of our previous reports.

PROFESSOR CHARO: Diane?

DR. SCOTT-JONES: I have a question. I may have missed this but did we get a paper that is referred to as background material for this central office. It is McCarthy?

PROFESSOR CHARO: Oh, it is from -- about the fifth month that we existed. I think we were still meeting at NIH in building 31 when McCarthy presented his paper.

DR. CASSELL: John Fletcher and Charlie McCarthy.

(Simultaneous discussion.)

DR. SCOTT-JONES: So it is cited at 2000. I thought it was something you were about to give us. It is footnoted as 2000.

DR. SPEERS: Then that is an error.

DR. SCOTT-JONES: Okay. All right.

DR. SPEERS: Sorry.

PROFESSOR CHARO: But it may be worthwhile getting fresh copies of those papers since I do not know what your office is like but in my office you would never find something from that long ago.

DR. SCOTT-JONES: Okay.

DR. MESLIN: Diane, you will recall there were two -- three papers that were commissioned. One from John Fletcher, one from Charles McCarthy and one from Tina Gonzales. Those are what those are referring to. McCarthy was proposing that OPRR remain within HHS. Professor Fletcher was recommending that OPRR at that time be moved outside of HHS. Professor Gonzales was given a different mandate but the McCarthy and Fletcher papers were seen as complementary papers to propose where OPRR should go if it goes anywhere.

DR. SCOTT-JONES: So those are now going to be included in Volume 2 of this report?

DR. MESLIN: Yes.

PROFESSOR CHARO: Arturo?

DR. BRITO: I want to express one concern that kind of arose off a little bit of what Bette was saying. Before I say this I want to say because -- Marjorie, I think I am the only one who did not say what a great job you and your group has done so I want to make sure I tell you this because it really is incredible the amount of work that went into this.

One of the things that I found here, and I know it really refers to the recommendation -- going back to 2.1 with the private funding research, privately funded research, is that I did not find enough ink in here to convince me, especially if I am an outsider especially in the private world looking at this. So I just want to make sure that there is going to be more attention paid to that area because I can just imagine this is going to be

quite -- not an easy task.

It is going to be quite controversial when we suggest this.

DR. CASSELL: That is another reason for going to those two papers and really literally take their arguments. They are very good in their papers.

PROFESSOR CHARO: Right. But, Arturo, just to make sure I understand you correctly. You mean the justification for extending --

DR. BRITO: Extending the --

PROFESSOR CHARO: -- the jurisdiction over to the private sector, which means the anecdotal reports about the way research goes on when it is outside of the current IRB review process entirely?

DR. BRITO: Right, exactly. Basically I am just saying we need to make it stronger.

PROFESSOR CHARO: Okay.

DR. BRITO: I think it is something we all agree with. We have been doing this for years, deliberating on this and talking about it.

PROFESSOR CHARO: So anticipate the congressional hearing essentially.

DR. MIIKE: I think the objection or resistance to that would depend because what we have learned, most institutions like universities that fund both kinds of research already apply the Common Rule. Most of the major pharmaceutical and genetics

companies that we have talked to voluntarily follow the Common Rule already.

And I think the objection would be more towards the paperwork burden that they might deal with, with an oversight committee.

But certainly I think a good case can be made that the leaders in the private side already are implementing it.

You are saying no but from what I gather from the major pharmaceutical companies, they do have IRB reviews, they more or less follow the process.

PROFESSOR CHARO: Well, because of FDA.

DR. MURRAY: Because the FDA requires it.

DR. MIIKE: Okay. Oh, okay. But that is -- I mean, the -- whether or not that is the case, they are already versed with the system.

PROFESSOR CHARO: The sectors that are currently unaffected, relatively unaffected, include biotech sector that is working in areas that FDA has not chosen to go out and regulate. So in the genetic testing area, for example, although FDA could probably get there through its regulation of biologics and devices, they have not, and so that sector has been relatively unaffected unless they use university based investigators.

Reproductive technology clinics and obesity clinics that exist outside of major medical centers that are, in turn, affiliated with university centers tend to be fairly clear. Surgical -- stand alone surgical facilities are another.

And so it is not pharmaceutical companies exactly that would be the likely, you know, surprise -- I do not know how to say this but who would not be the most likely people to object.

DR. BRITO: Right. Can I just respond because even if -- I mean, there are a lot of companies out there, a lot of people in the private world that do not necessarily have to follow regulations that volunteer anyhow, and we know that. But I am just worried about the perception that this is going to create this extra work and it is actually, you know, to show that it really does not necessarily create extra work for those already following the rules voluntarily or as they are supposed to.

PROFESSOR CHARO: Okay. No, no, I did not mean to cut you off, I was just --

DR. BRITO: That is it. That is it.

PROFESSOR CHARO: -- who is on the list.

DR. BRITO: Even if it is just a perception, people are volunteering -- that is just -- that is one of my concerns here that we are going to get a backlash of complaints about this.

PROFESSOR CHARO: Okay. Tom and then Bill?

DR. MURRAY: Arturo's point is very well taken because there may be some pockets of resistance to this proposal. It is probably not going to come from the organizations which already are comfortable with it and I would guess even probably find it in their interest to, you know, do this, follow the rules on human subjects protection.

It is a question -- let me pose it as a question to

Alta. The folks who do supplements, which are largely now exempted from FDA review by 1994 law, but constantly report research as to the efficacy of their supplements, I take it they would not currently be covered unless they did it voluntarily or through a university with an MPA. And that they might take --

PROFESSOR CHARO: Correct.

DR. MURRAY: -- they might take great exception to being covered by these rules. I am speculating on the latter.

PROFESSOR CHARO: Correct. They might take exception.

DR. MURRAY: One of the chief defenders of them happens to represent a state in the U.S. Senate.

PROFESSOR CHARO: Yes, that is another sector I had not thought about. That is right.

Bill?

MR. OLDAKER: As to additional burdens, I think that if -- and I think that is something we should worry about. But I think one of the things is we want to see stronger IRBs, better educated IRBs, and place some of the direction here from the new agency to help them in their educational mandate.

I think that if that is done I think that that will -- and it is not that everything has to be approved ahead of time by this agency. It is just that the IRB has to comply with certain guidelines and I think that if the risk is of that IRB losing its certification then you will have the right kind of pressure applied.

The second thing, I agree with Bette. We do not want to

take back. We do not want to disarm the Federal Government in some of the powers it currently has to deal with universities and others. I think that those are almost thermonuclear devices, though, at times and they can only be used so many times and then it becomes very hard to get adequate enforcement if that is the only thing -- the only tool that anyone has.

As to the other types of companies I think that actually we would find that the privately run IRBs are much more prevalent even in the biotech community and I think that most companies do employ them now. If for no other reason than for self-protection because they are looking for a way that they can have a check on what they are doing and that they can have a secondary opinion outside of their own organization as to how they do their research of various sorts.

So you are right. I think the supplements will be an enormous problem. I think as long as we keep the paperwork down I do not think there will be as much resistance as people might perceive that there might be.

PROFESSOR CHARO: Bernie? Sorry. I am sorry. I have actually got a list here. Wait a second. Trish, Eric Meslin and then Bernie.

PROFESSOR BACKLAR: I actually have a concern about the kind of research that goes on. For instance, the cosmetic surgery research where the -- somebody I think in New York City -- you cannot hear me? You can now. You know the research that I am referring to. A plastic surgeon in New York City did one kind of

procedure on one side of the face and one kind of procedure on the other side of the face but did not tell the patients that actually he was doing research and seeing which was going to come out best.

What concerns me, of course, is that this kind of thing -- how one can bring all of this into the loop and how will people like this know about this report? I mean, I am actually really very concerned about certain private research which will be hard to get to until something has happened.

I do not have a solution but that is a concern and I think it is something we should think about.

I thought the issue about closing down the universities I thought actually you -- Marjorie, you spoke about that very well in here because that -- yes, it is certainly a deterrent but it may in some cases be too much of a deterrent and be actually harmful to research. One would want to find ways to deal with it so that that did not have to happen.

PROFESSOR CHARO: Eric?

DR. MESLIN: I just wanted to remind commissioners again that two meetings ago Bert Spilker from Pharma did testify before the commission indicating his support for the idea that the pharmaceutical industry would be more than happy to comply with subpart A of the Common Rule and then he referred to other areas of concern that they might have.

So it is an empirical question as to whether everyone in the pharmaceutical industry is or is not, or is doing it

voluntarily or is doing it for reasons other than reasons that universities might be wishing to comply.

I do think, though, that his statement is very important because it is the first time that they did testify publicly that the rules that are used for publicly funded research would be seen at least for parts of the federal policy as being something that they would be willing to support.

We have had other discussions with them and others which show other areas of worry or concern but I do not think it is as cut and dried as everyone in the private sector, leaving aside all of these other items the mainstream public sector are now complying voluntarily.

PROFESSOR CHARO: Bernie?

DR. LO: I think the idea of trying to anticipate where the resistance and opposition is going to come from -- you suggest a controversial public policy is a very sound one. I think this discussion is very useful in trying to anticipate what are the kinds of concerns and objections and kind of address them up front rather than sort of not being in a position to respond once the report is written.

As I step back, it seems to me there are a couple of issues that are of concern. One we have already talked about which is the paperwork burden. The other is really the delay, the perceived delay in having to get IRB approval because of the cumbersome nature of the IRB process. And, you know, part of this obviously is the growth of independent IRBs.

But I think we also -- I think it would be good to sort of think about that, both in order to address it in the report but also to think through as we put together a package of recommendations whether, in fact, we have done what we can to make the paperwork no more burdensome than it needs to be and to cut back on delays on the types of research that really do not present a whole lot of risk.

It strikes me that what we really want to do is go after the types of research that have a higher probability of causing serious harms at least to start out with because I think if it is perceived as sort of having a lot of delays for research that by and large is not very objectionable, people are going to say why are we -- what is the purpose? What is the point?

So I just want to be careful that it is not just the paperwork but it is the perception of delay and sort of going back and forth. Some of this we are going to address in some areas with the multi-site research recommendations but every time we can sort of think of that we should keep a list and then come back to it at some point in the report.

PROFESSOR CHARO: Diane?

DR. SCOTT-JONES: I just have a question. I agree with what Bernie has just said but it seems to me that the central office, if we are still focusing on that, would not have any real bearing on what people do as researchers when they go to apply to their own IRB because the central office is going to be very much removed, right? The central office would not have any influence

on what happens on a day-to-day basis because it is to work through the existing agencies and through existing parts of the private sector. It is not going to have any bearing on delays at that level, will it?

DR. LO: Well, but by setting policies and guidance it can either make things slower and more careful or speedier and --

DR. SCOTT-JONES: Indirectly.

DR. LO: Yes.

PROFESSOR CHARO: But the more that the guidance gives clarity, the more choppity chop the review can be and some things can get through very quickly. Right? The more that there is clarity there.

DR. SCOTT-JONES: So it could have a positive effect on delays. It would not necessarily --

PROFESSOR CHARO: Absolutely.

DR. SCOTT-JONES: Because you are never sending anything up to them, to the central office.

DR. LO: Right. I think what we need to do is say that as we provide this guidance, not just look, look real carefully at this type of research, but there are some types of research where we really would not make it easier for investigators and IRBs to sort of have the review done in a way that is not very, very easy.

PROFESSOR CHARO: Bette?

MS. KRAMER: To go back to something that you said earlier, were you suggesting that we should consider -- we have

talked sometimes about a centralized IRB. Were you considering -- were you raising the possibility of that being a part of this office?

PROFESSOR CHARO: Yes, I did want to make sure that we kept that on the table although we may want to push that off so we can move on to the next recommendation but, yes, the -- periodically we have come up with suggestions that for certain very isolated functions it would be very helpful to have a centralized IRB and this would be a natural place to house -- or have this office be capable of assembling such a beast when needed.

MS. KRAMER: Now if you push it off the table, does that mean we are going to come back to it?

PROFESSOR CHARO: Yes.

DR. SPEERS: I just want to jump in here and say that one time we could come back to that would be tomorrow in Chapter 4 when we are going to be talking about review of multi-site studies, the issue of central or lead IRBs come up at that point, and I think we could also pull in that point.

There might be two issues here that Alta is raising. One is, is whether there is some types of research that would benefit from a more national type of review. This would resonate with you with the capacity report where you recommended a standing panel.

The other issue -- I did not know if you meant this, Alta -- was sort of as an appeal to IRB.

PROFESSOR CHARO: I meant both.

DR. SPEERS: Okay. Then I think we could bring that up tomorrow in that discussion and we will just be sure we do.

PROFESSOR CHARO: Let me -- because again I am trying to watch the clock, although we are actually doing very well, I want to make sure that there is plenty of time to talk about what comes next because I have already heard people suggest that they have got issues with it.

Let me take the privilege of the chair just to point out that there is also a natural segue issue here.

To the extent that the system continues to rely on people presenting themselves to an IRB for review, it means that people have to know that what they are doing is what is considered to be human subjects research. And that has been a challenge even within current structure, even in places like universities where you have regular faculty meetings and lots of opportunities for casual and formal education, and a fairly small organizational structure, right, and still we find many investigators who do not perceive themselves as having done human subjects research and have not even presented themselves to the IRB.

The IRB does not even know the stuff is going on. All right. And they are shocked. Shocked when they saw that they have been out of compliance.

At the moment that we extend this to the private sector, which as Eric has pointed out to me is routine in other countries, we have to realize that that problem becomes to get even more

complex because there is not yet any culture of expectation in that sector of needing to be reviewed and the areas in which there will be genuine confusion as well as an incentive to remain confused about whether what you are doing is human subjects research seem to be vast and we have heard about the car crash tests. T here are all sorts of consumer and marketing -- market testing that would not seem to be automatically excluded by most kinds of language that we could possibly come up with, et cetera.

So I think it is going to be very important not only that we have a definition of human subject but in the context of this discussion, I would urge us also to think about ways in which we can help this central body to carve out identifiable areas that are not going to be considered human subjects research for the purpose of these regulations.

But it may be as simple as offering every member of the United States an opportunity within the next six months to present reasons why his or her business should not be included and put it on those people to make the case and then issue a set of rules every year updating it on these are the areas that are not covered. But we have got to make sure that that is included so that you have both inclusionary criteria and exclusionary criteria.

On the inclusionary criteria I know that Jim Childress already has indicated he wanted to talk about this and let's start there.

DR. CHILDRESS: Since I was late this morning and did

not get to thank Marjorie publicly, I will do so now to join the chorus of praise.

Actually the question I want to raise about this is really a step back question because what I would like for us to think about -- and this came to me in sort of reading through this whole -- is one possible impression -- one possible story one could tell about why we came to this point, and I worry about the implications of where we are now.

There is a -- in the regulations there is a model or a paradigm of interventional biomedical research that several people in the social sciences have told us is a real problem if we just sort of extend that into the area of social sciences. And as a result we have a paperwork burden, we have IRBs concentrating on less risky research rather than risky research. That is one way to talk about the past.

What happens in this particular report then is that we move to a broad category of common elements. So collection and analysis of data where there is no intent to benefit participants with those data becomes sort of the defining element.

And the worry that I would have at this point is that actually if we follow that through and do not do more than we have done here, we will end up sort of putting everything in the same level again and not paying enough attention to the risky research.

Because if you look here, the interventional biomedical research does not play much of a role in this discussion. Again I

think there are good reasons for going in the direction we are going but I would at least like to flag that in terms of the way this report as it is currently written in this part is likely to be received because we then downplay what we have already considered to be the riskier research and we have put everything now on the level of -- just think about it -- analysis and collection of data. That becomes our category. Where there is no intention to benefit people from whom we obtain the data.

And that really is taking the common element to be -- I mean, it is a common element in all the things that we are talking about but it is to put it on the level where what gets emphasized then is really what is most critical in the social scientific arena.

So let me just flag that as a concern and that is in no way to detract from what is here but at least to this -- reading this, posed for me the question as to how we could make sure in the final analysis that we ended up with a concentration on what is riskier, what is most important and spend less time in real life on human investigations and IRB reviews.

PROFESSOR CHARO: Bernie?

DR. LO: Yes. I want to follow up on Jim's comments, which I think are very wide. I mean, there is different kinds of activities we want to deal with. At the simplest level it is just the analysis of data that has already been collected and you are just going to kind of reanalyze it.

Then there is sort of collection of data where it is

really a pretty passive thing that you are just observing or collecting data that is going to be around anyway and you are just sort of catching it in a systematic way.

And then there is manipulation or intervention and that is the classic biomedical paradigm. It is not just that I am analyzing data or collecting it but I am doing something and something usually invasive to the participant which may carry significant risks of serious physical harm.

And it seems to me although, you know, we have been -- you know, Jim was pointing out, you know, we are trying to both have a policy that applies to all kinds of research and be mindful of how research is done but we also need to say that by and large many of the scandals in research are biomedical interventions. For every, you know, sort of social science research that has raised people's hackles there are many, many more sort of very serious physical harms where people were not informed, the risks were way out of balance, there was no possible benefit.

So I think in the very definition of human participants research it may be good to sort of carve out a separate category of intervention. We do that in the second page where we say intervention may mean data collected or manipulations. But I just think that if we think about analysis of data, collection of data and subjecting a subject to -- a participant to a physical intervention you begin to sort out different kinds of research with very, very different kinds of risks. And, you know, obviously one project can do all three but I think that might help

us sort things out.

PROFESSOR CHARO: Bill?

MR. OLDAKER: I agree with both Jim and Bernie. In fact, I did not think it was practical to argue that this be limited to biomedical research, if it were, I would be in favor of that. So my theory was to try and limit the enforcement to basically abuses in biomedical research where harm could or did come to various research subjects.

And if that were done and then basically you -- you are basically segmenting it by the way that the law and the regulations would be enforced that would be having the same effect. I basically viewed myself as a voice of one saying that I would be in favor of making this as narrow as possible at the front end because I think that the narrower you can draft these, either statute or regulations, the more likelihood you can have for some success in their actual implementation but I had not heard any others take that position.

PROFESSOR CHARO: I had occasion this morning to share with Marjorie a reaction I had to Recommendation 2.4 in light of what I was reading later in Chapter 3 when we were struggling over the characterization of the components of research. It may be a hobby horse of mine but I have never -- I have never been persuaded that it is the systematic collection or analysis of anything that is really the key variable that ought to trigger this whole panoply of federal interventions but it is something about the fact that the person who is now the research participant

is -- has become secondary, that there is some primary purpose that lies elsewhere. And even in the interventions that are possibly therapeutic in a biomedical context, the fact is that the research participant has become secondary to the larger value of providing information to society and new knowledge for science, et cetera.

And it is that phenomenon that in my mind triggered the urge to say, okay, if somebody is going to be placed in a position where they are now to some extent a means rather than an end, that it is appropriate to have some extra layer of protection. And that layer of protection is most urgent where these individuals would least expect to have become means rather than ends, which is why the biomedical situation seems to be most compelling. It is where it is most -- people are most easily confused and they think that they are really the primary focus of the professional's interested.

In fact, no matter how benevolent the professional is, the primary focus lies elsewhere as in bettering knowledge for the future and this person's betterment is a desirable but necessarily secondary goal.

And I found myself wondering if we can try to rephrase it slightly so that we emphasize that being a participant in research means being somebody who is either having a physical intervention or is having his or her environment manipulated or somebody about whom information is being collected where the primary purpose is to better society or to advance science even if

a secondary purpose is to better that person.

And then move on from there to try and decide whether or not we want to then have distinctly different regimes for the three kinds of interventions or, as has been done so far in this report, attempt to have regimes that are the same for all kinds but are flexible enough that in application they would function as if they were distinct regimes.

Eric?

DR. CASSELL: Well, first of all, I want to say I think that is absolutely right and it is the characteristic of research. It is not the data. It is not the systematic. It is the place of the participant in relationship to the investigator -- to the enterprise. And the care of the participant and the patient is primary. In research the participant is secondary to the acquisition of knowledge.

We certainly hope they are going to be because otherwise the acquisition of knowledge will be injured.

The importance of saying it is not only that it simplifies the understanding of what we are after but also so that investigators get it through their head that if they say to us, 'Well, my patient comes first,' I want to say, 'You are fired. You are not doing the job you were meant to do. You were meant to collect data and so forth.'

It keeps being a problem. So I do not like the other things about theories and all that kind of stuff because I think it just gets too complicated but this point, whatever the

definition, I think should be up there in neon.

PROFESSOR CHARO: Well, it may have some implications for how it is that we expect certain kinds of anthropological or oral history interactions to be characterized as a result.

DR. CASSELL: Oh, but isn't it true in that also? Don't we -- we do not -- I mean, my oral history subject or participant is tired. Right? This is my one chance to get that oral history. I do not care about tired. I care about the oral history.

PROFESSOR CHARO: Let me take a comment from Trish and then suggest that since people are beginning to dash, we clearly seem to need a break earlier than 3:30 so we will take a break now and then we will come back and finish up.

PROFESSOR BACKLAR: I just wanted to second your comments. And also particularly, as we move, using the term "human participant" rather than "subject" because "subject" said that that person -- people did not like it but it said what it was. It says it as it is so to speak and we may want to even make more of that. Why we have moved. But we still do not know. We know that those people are really being used.

PROFESSOR CHARO: On that cheery note, it is 3:06. Why don't we try and get back here at 3:25.

(Whereupon, a break was taken.)

PROFESSOR CHARO: We were in the midst of discussing how we would like to characterize human participant research. So far there has not been any objection to the idea that it makes sense to try and combine the notion of human and participant -- human

and research into a single definition as opposed to having the two part definition that currently exists in the federal regulations.

But we have been struggling a little bit about the correct way to characterize this in a way that will sweep in the right things for federal regulation and to keep out the things we do not want to have regulated.

The floor is open to anybody who wants to add conceptual clarity or anybody who wants to take a stab at language at the risk of doing a little bit of group writing, which is always very time consuming.

Larry?

DR. MIIKE: A related issue. I guess what we have opted for is a broad definition of human subjects research to sweep in under the purview of IRB review and then on the back end or once you do that trying to filter out the kinds of things that should not be of any concern.

I think we need to make that statement up front when we start in this area because without that people are going to say look at what the commission did. They just totally expanded the scope of the human subjects research and pulled in all of these kinds of things that it should not have any concerns about.

So I think we need to make that statement and then, of course, the second part of this definition I do not agree on pulling in the related individuals.

PROFESSOR CHARO: Right. And we will absolutely get to that. We have got about another hour-and-a-half before we are

scheduled to adjourn today so we will absolutely get to that.

Bernie, since you are the person who frequently suggests the helpfulness of concrete cases, would it be helpful to try and agree among ourselves on the -- one some examples of things that we want in and want out so that whatever language we get we can test. There are certain kinds of problematic areas that we have encountered repeatedly and we might want to just be clear about.

DR. LO: Quality improvement and disease management and the overlap there with health services research. Marketing, business planning studies, again do the same thing. You project what your needs are. It is classical epidemiology in some sense.

Going back to what Eric said before the break, if the defining characteristic is that the focus is not on the individual per se but on the success of a project or the goals of the project then, you know, all those activities are similar to research in the sense that you are not focusing on the well-being of the individual. You are focusing on something that comes out of the aggregate knowledge.

If we adopt a definition of research having to do with intervening on people, collecting data systematically or analyzing data that is already collected, again it seems to me those sorts of activities would fall within the gambit of research as opposed to say clinical practice. Now you have this funny business -- core business operation concept, which, you know, seems to take that out saying I can do whatever I want because I need it for my

business to survive and that takes priority over the well-being of -- concerns over the well-being of participants. But it seems that is exactly the sort of situation where you want to try and have some protections built in.

DR. SPEERS: If I may add to the discussion because I think there is another defining piece in this but you could look at what the IRS does. Their primary focus is not necessarily the benefit of the individual but the IRS may not do research. There is -- what the census -- the data that the Census Bureau conducts or collects, whether that is research or not research.

Journalism is one that we have talked about in the past.

So I think what these examples, in part, do is get to another defining criterion, which relates to the type of information or the intent or the purpose and the use of the information.

PROFESSOR CHARO: And the characterization would be?

DR. SPEERS: In the current definition it is the intent to generate generalizable knowledge or what we have talked about here, to generate knowledge -- new knowledge or revise knowledge that contributes to science and to theories and principles.

PROFESSOR CHARO: Eric?

DR. CASSELL: Well, the trouble with new and so forth is we say it is not new if it is not new and we -- it is a statement about something that is testable. It is a testable statement and it should not require a test. Is this really new knowledge? It

does not matter whether it is new knowledge. We generally talk about it as generalizable knowledge and so I do not think you have to say new knowledge.

Mostly we also talk about a systematic -- so it is not in one individual case. On the other hand, there are single case studies and once again those patients have to be -- those participants have to be protected so that that part of it fails. It certainly does not matter whether it is used to devise or revise the scientific principles and theory since any good knowledge ultimately does do that or at least has an impact on them.

So I think it fails each one of these tests. It does not fail your test. None of these fail your test in this -- that is the point.

PROFESSOR CHARO: Well, no, I mean what I was describing before I think has a very big problem with it. I mean, focusing on people being means rather than ends does not provide an easy way to exclude a variety of things that we do want to exclude here. We want to exclude journalistic interviews. We want to exclude marketing research, I think. I think. Do we? That was my purpose in asking Bernie about do we want to.

DR. CASSELL: Well, once again those things collect systematic or generalizable information.

PROFESSOR CHARO: Well, so far --

DR. CASSELL: Marketing research does for sure.

PROFESSOR CHARO: Let me give you -- when I was -- years

ago when I was a student, I volunteered to be part of a focus group in which we looked at different silhouettes of automobiles and we were asked to evaluate those silhouettes in terms of aesthetic quality, our instinct as to whether it was an American car versus a European or Japanese car. I mean, it was market research, right? And would you want me to be considered a human subject of research for that? You know, would you want that to be subject to federal regulation? I think this is a better way to ask this.

DR. CASSELL: That one not but how about the one in which you are not informed about what you are doing so that you are a participant in research, market research, which you otherwise would never have chosen to do because of the subject of it or because of what it is going to be used for?

PROFESSOR CHARO: As in?

DR. CASSELL: I mean, I can think of research where people are choosing products that it looks like they are choosing one kind of product and really it is related to some sexual material that they do not even know about. It is put across as one kind of research, one kind of set of products, when it really is used for a different purpose and you do not know that.

PROFESSOR CHARO: My mind is just racing to come up with --

(Laughter.)

PROFESSOR CHARO: What exactly are you talking about?

DR. CASSELL: If your mind races, I have made my point.

(Laughter.)

PROFESSOR BACKLAR: Is this in the transcript?

PROFESSOR CHARO: It is all in the transcript along with the whips. Bill?

MR. OLDAKER: Although I find it exciting, I would be opposed, I think, to having any market research covered in what we are trying to do here. Enough said, but I would like to see this as narrow as possible and so, you know, I do not have to state this every time, I guess, but you know as close to biomedical research as possible. And I realize that I will not win solely at that level. The farther you get away, I think the more ambiguous enforcement will become.

PROFESSOR CHARO: Why would you want it narrow as opposed to what Larry said, which is the alternative of being very broad within clearly written categories that -- I fear to use the word -- "exempt" certain areas from federal oversight.

MR. OLDAKER: I think that is where we will end up and I can live with that. I think, though, if you start off with a smaller net that it will be easier for people to know what their responsibilities are under the law and the regulations. If you do kind of -- and Larry said this as an aside -- you do a large net at the beginning and then narrow it in some way as you go along.

I think that is okay. I personally do not find that preferable but I think that it accomplishes some of the same things.

PROFESSOR CHARO: Eric?

DR. CASSELL: Well, I understand that if you put it so wide and you just diffuse out the -- whatever this agency's efforts and so forth, but that is what exemptions are for.

MR. OLDAKER: What is that?

DR. CASSELL: That is what exemptions are for.

PROFESSOR CHARO: Larry and then Bernie.

DR. MIIKE: I guess I still have to go with the wide net but it does not mean that the system does not evolve over time. And that is why I do not think we should dismiss the whole issue of exemptions at the beginning here because I think over time -- I would guess that aside from the convoluted exceptions in the current rule, which is sort of hard to figure out what the rationale is and understanding it, there seems to me -- there are going to be whole categories of research that are not going to be controversial and that can begin to list a whole bunch of exemptions. So I would like to include that in that way.

Another way to deal with the definition of human participants research is that there is nothing to stop us from introducing the notion of risk.

DR. CASSELL: Say it again.

DR. MIIKE: Introducing the notion of risk into the definition. And since we already talk about minimal -- I know nobody will buy this but since we talk about minimal risk as a threshold, what if we say there is not even minimum risk. You know, if you have a human participating in the system at collection of knowledge, et cetera, et cetera, but there is no

risk -- you can either say we exempt that or we do an expedited review, or we say that is not research. That is not human participants research. Because it is an artificial construct that we are developing here anyway. I mean, a lot of people would say what are you talking about, human subjects research when I do a survey. You know, I mean, they have a much more concrete notion of what they mean by human subjects research.

I know nobody will buy the idea, or maybe you will, about introducing the concept of risk into the definition, but my main point is that we seem to be going along the line of a wide net but we need clearer direction for whoever is going to take our implementation seriously about how we make it a more handle-able system.

PROFESSOR CHARO: Tom and then Jim?

DR. MURRAY: I continue to marvel at the ability of the commissioners and staff to reveal hidden complexities in things which seem to be relatively simple and straight forward for understanding. I mean that as a compliment. I am not being ironic here.

Thinking about the market research example might be a fruitful one. We call it market research. We use the word. Of course, if a company is studying the silhouettes the last thing they are going to do is share that with their competitors. So it is by no means in the interest of generalizable knowledge. It is instrumental knowledge for some particular purpose. Here a commercial purpose.

Whether we could use that notion of intent or not, I do not know. If the same study were done in a marketing department of a business school and published, then it is research. It is human subjects research. It is exactly the same study, exactly the same kind of population, there is a difference in intent and audience.

I do not know if that is helpful at all.

PROFESSOR BACKLAR: That is what Mary Durham said when she came. We had a long discussion about the issues of intent.

PROFESSOR CHARO: Jim?

DR. CHILDRESS: Building on Larry's comment, I guess I am less concerned that we build an element of risk into the definition. I do not mind, as Bill was conceding also, a fairly wide net at the outset. But I am interested in the kinds of mechanisms we have in place, the triggers that we build in later, for signaling why we want certain attention to certain kinds of things. And what I worry about, as my comment earlier suggested, what we have here is that I think too many things get brought in and it is not clear in this report exactly how one can sort them out then. Because, in part, it is a matter of priority what IRBs spend their time on, what kinds of things get emphasized and so forth. I think risk is certainly one way to do that but we probably need to do more than we have here if we are going to go in that direction.

PROFESSOR CHARO: Trish?

PROFESSOR BACKLAR: No.

PROFESSOR CHARO: Would it be possible to try and keep the definition and the notion of risk closely linked but nonetheless somewhat -- keep them disentangled by defining human participant research in a broad way? I mean, basically it is anything that involves interacting with humans or gathering information about humans where the primary purpose is to develop information that will be for the benefit of others. Right? And that this definition also means that even if the humans themselves are potential beneficiaries of the interaction or the information gathering so long as the first purpose is to benefit others that becomes -- then it is human participant research.

Having said that, the next thing is the Federal Government wishes to regulate human participant research under certain circumstances and those circumstances include situations where the humans are likely to be confused or misled about the fact that they are now the subject of study and where there is little -- we can actually -- I am not even sure where the list would go, I mean. And as a result we are going to exclude certain areas and that gives us the opportunity to easily make a list of exclusions that is -- it is a series of examples and this omnipotent central body has the ability to continue issuing guidance that will clarify additional areas that are excluded so we can quickly list things like journalism and quality assurance, and educational evaluations.

I think that we could debate whether we would like them to put oral history on the list, you know, but basically it is a

list of examples and it is up to them to keep adding to that list.

And then the next thing that would be said -- then the Federal Government takes the position that some of the remaining regulated areas are going to be distinctly more problematic than others in terms of the risk they pose to people, both physical and psychological or even socioeconomic. And, therefore, the regime that is proposed is one that tries to quickly dispose of low risk research by an administrative review that identifies those low risk and allows the investigator to move on.

We might want to even rethink the issue about the waiver of informed consent to make it easier to waive consent as now written. There is a presumption of waiver of consent unless it is not feasible. And we could change the presumption.

And that way -- and in this sense we keep these things closely linked because we are talking always about why the Federal Government is in this business but we keep the issue somewhat separate so we can write them clearly. I do not know if people think that might be a productive way to try to approach this.

DR. MIIKE: I think that is the only way we can go. I think that what we need is to stop and say conceptually it is easier to have an inclusive definition of research instead of starting at the beginning without any kind of algorithm in our heads or any kind of lead information about how one would define this and already exclude certain kinds of things which would commonly fall into this area.

Then we look at -- like I say, defining things as human

participant research does not necessarily mean that all of it gets regulated or that it is regulated equally. And that since we have the experience of the past 20 years and even if we do not agree with the way that the exemptions were developed, common sense tells us that within this universe of human participant research there are categories that should have the presumption of exemption or should be exempt, and develop a system like that of saying that.

And the criteria you use is the degree of risk, invasions of privacy and confidentiality, whether a participant knowingly participants and consents to research. Those kinds of things which are already built into our system that we have. I think we just sort of have to approach how we present that in a different way.

So when we look at it we say, okay, we are talking about transforming a system and if we are going to do that we are both being inclusive but we also want to begin to start the process of focusing down on those areas of real concern. If all we do is reorganize the system and make it inclusive we are going to make the system worse because then you do not know which things are important and we not going to begin giving any guidance about which kinds of things are important.

PROFESSOR CHARO: Eric?

DR. CASSELL: I had just -- it may be a step backwards but the answer to what is research must be -- there must be 20 definitions of research. We must have definitions of research in

previous --

PROFESSOR CHARO: The text has about six of them presented for us, yes.

DR. CASSELL: Yes. I personally -- I would not mind just seeing this set of definitions that have been used.

PROFESSOR CHARO: Well, let's take a moment then to take a look at them. I think that page 20 or so --

PROFESSOR BACKLAR: In Chapter 2?

PROFESSOR CHARO: It is in Chapter 2. I remember, you know, there were some dictionary definitions.

DR. SPEERS: It starts on 22.

PROFESSOR CHARO: Yes. So it starts on the bottom of 22 and continues on to 23 and then even into 24, 25. Yes, you definitely gave us lots of text on this. I mean, we are hitting on all the elements. We just have not agreed among ourselves on how we want to use them and the elements include what is being done, to whom it is being done, what the intent of the doer is while the doer is doing it, how the -- how whatever is done is going to be used later seem to be the key factors that are mixed and matched in these definitions.

DR. CASSELL: On lines 3 through 5 on page 24 --

PROFESSOR CHARO: The current federal regulation? That is the current federal definition.

DR. CASSELL: Yes. But what if the research of the kind we are interested in falls outside of that?

PROFESSOR CHARO: Well, most of people I know in social

sciences find that this can be problematic because they are unclear of how systematic it gets to be, what constitutes generalizable knowledge. I mean, I will give you an example. I will give you an example.

A friend of mine was going to South Africa and she planned to interview the members of a gender equity commission there as part of an overall project on the development of gender equity in South Africa. And she knew all these people personally. They were friends. She often sits around talking with them so she was going to go to South Africa and just make a point of trying to see all her friends instead of just only one or two.

And the question was whether or not this was suddenly human subjects research on her friends as opposed to being research on gender equity in South Africa for which she was just interviewing some people to get information.

And because of the lack of clarity in that definition for a situation like that she found herself going before the IRB at our institution that handles the nonbiomedical research area because we have got so much research we kind of divvy stuff up. It is an IRB that is notorious on our campus and it took -- I think it took a couple of months to get through and they focused on consent forms her friends would have to sign acknowledging that they might be named in her research and things like that.

So now this was the question: Do you want that covered or not because, in fact, yes, she is going to be interviewing people who may be quoted and cited by name? Is that something

that now is the area that we generally want to have federal oversight and then let an IRB sensibly review it and try to make a sensible determination? Or do you want it kind of outside the bounds?

DR. CASSELL: Well, you said she was doing that in order to study the larger question of... Once you say the larger question of...you are talking about generalizable knowledge. I thought that the way that this report handles that is not by trying to make a definition that solves every one of those problems but by trying to get rid of work for the IRB that it does not have to do.

PROFESSOR CHARO: Okay. We have got Jim, Bernie, Arturo, Marjorie.

DR. CHILDRESS: And if we take your example, it seems that we still face the same problem with the definition that is present in this report. That is you are still going to have to include it and then you are going to have to ask, well, how should you include it, should you exempt it, should you give expedited review and so forth. I mean, your focus is on this definition in the current regs but wouldn't our current definition force it in as well?

PROFESSOR CHARO: Well, the current definition is still up for grabs.

(Simultaneous discussion.)

DR. CHILDRESS: But that is the reason for raising the question about the current definition.

PROFESSOR CHARO: Marjorie would like to intervene. Yes?

DR. SPEERS: Only just to maybe perhaps clarify with the example that Alta gave.

There are two issues that the social scientists have raised. One is the definition issue and the other is the review issue and I think that we were hearing both actually in your example that, okay, while there may have been some disagreement about whether it is research, even if it is classified as research, it does not get reviewed appropriate for the type of social science research it is. It gets reviewed under the current set of regulations, which is more clinically oriented is the issue.

PROFESSOR CHARO: That is correct. There are two issues. Is she doing human subjects research or is she doing political science in which she is just talking to people? She is not studying the people. She is studying the country. And, second, absolutely, whether the IRB reacted.

Bernie, Arturo?

DR. LO: Not matter what definition we finally adopt it is going to be over exclusive for some and under inclusive for others. I think we just have to acknowledge that and live with it.

I would strongly favor we make a definition and then very quickly exempt or provide exceptions for things that we are pretty clear about. It is not just, I think, making a list. What

bothers me about the current federal regulation is it is like a list -- I am not quite sure why some things are on it and other things are not.

So what is missing is sort of a justification of why are all these things -- of all the things in the universe, why put these on the exempt list? We have started to come up with some of the criteria that we -- you know, it seems to reason that you would exempt something if there is no concerns about privacy and confidentiality, which strikes me, Alta, your example does raise some concerns. You are going to quote people by name. They can be identified. You know, there may be -- there may not be -- repercussions. So you might want to look at that a little more carefully.

Larry introduced the notion of risk. I think that is certainly relevant to how much scrutiny you want.

The other thing is how easy is it for people just to say no. I mean, all the time we get phone calls asking to be in this survey or that survey. That is not a problem as long as, you know, it is pretty clear on the ground rules so I can just stop talking and hang up the phone.

It may be a little different if it is my doctor who is trying to force me to, you know, participate in the study.

So I think that -- and then we do not have to do all of this here. I think what we can do is sort of say we do not want to include everything in the world. These are some of the things we wish to exclude. These are some preliminary thoughts on why

the justification -- what the justification is for excluding these things. Let someone else work this out but at least get us started in sort of having a definition that has some advantages over what is there now.

Even just to say we think that certain things ought to be out as a matter of exemption or exception or exclusion right after we make the definition would be useful because there are a lot of things now as we have sort of said where IRBs are genuinely not sure they are supposed to be looking at this at all or not. So I think we could help them.

PROFESSOR CHARO: Arturo?

DR. BRITO: I admit I am a bit lost here with this discussion because I forgot where we are coming from and where we are going and I am not sure I am alone here. But I am just going to off the cuff tell you one of the things that I am seeing occurring over and over is the interpretation of the word "systematic" for instance. To me, as somebody who is a clinician that has taken a statistics course, when I hear the word "systematic" I think that that means that you are going to make sure it is statistically valid in some way, that you collect data in that way.

But I know that your friend who is going to do this research, she -- or this investigation or this survey, whatever you want to call it, systematic means -- just that. An organized fashion of collecting data.

So I think what is missing in this definition, and in

the text on page 26 -- which by the way there are other definitions of research there at the top, the Belmont Report, et cetera, but it is the third point in the second paragraph on line 15 about the validity of what is learned. So somehow this is related to the systematic collection of data, et cetera. And I have no idea where I am going with this because I am just totally lost but I know somehow this is an important here that the interpretation of different words, even within a definition of research, whichever one you use, is so varied that it gets very confusing.

So I do not know. Just something to consider but I have not heard -- when other people hear the word "systematic" do they hear implicit in there is that there is some statistic validity -- there is a test -- no, most people would not do that but I think it is --

DR. CHILDRESS: You have systematic theology, systematic philosophy, et cetera.

DR. SCOTT-JONES: Anthropology.

DR. BRITO: Right.

(Simultaneous discussion.)

DR. BRITO: I recognize that.

PROFESSOR CHARO: Exactly.

DR. BRITO: But see, we are talking about medical research because when you are collecting data there are randomized ways of collecting data and there are systematic fashions of collecting data and those are two different but, you know,

systematic can still lead to valid results statistically. So where are we going? I will leave it at that.

PROFESSOR CHARO: Eric, and then we may have to just settle on a game plan rather than on the actual definition.

DR. MESLIN: I am going to just make a suggestion in the optimistic hope that I can help Arturo not be confused.

There may be two things going on and that is why it may be confusing. One is the search for the elusive definition that 20 years of research ethics, scholarship, seems to have not produced a comprehensive and systematic internally and externally valid set of words for. The other, which I think is the principle purpose of this chapter, is to be able to describe what counts as an activity that falls within a range of concern and that range of concern may have several layers. It may have a concern of what counts as research for purposes of just not being something else, what counts as research that is going to be regulated, what counts as that activity that is going to be reviewed. Thinking of this as an onion skin.

And I think the challenge -- I mean, Colin Thomson pointed it out to some of us at the break -- that a lot of national commissions have had is to on the one hand come up with a -- in a sense a philosophically rigorous definition that is reforming or in some way stipulative so that people now get it and it is clear.

And when they cannot get to that point, as the President's Commission could not with the definition of death,

they come up with criteria for the determination of the activity that they are worried about. In our case we want to do both things. We would love to have a great definition and we would love to have a definition of a thing that once you know what it is you know what you are going to do with it like review it, like put it under the umbrella of human subjects or human participants research.

I think there is -- in the paragraph that you focused on, Arturo -- I think there is an element of the secret by listing not only these three common themes, which may be seen as the elements of a definition, they could be something else entirely, but I think that is where the most important transition for this chapter should be. The very fact that you have an idea of what systematic means and others might think something else does not turn out to be necessary to resolve it in my view.

If the commission is able to say we understand that the criteria for defining this activity have the following essential features to it then the more of those features that this activity has, the more convinced we all are that this is the activity that we want to have regulated.

I do not think -- unless you want to spend a lot of your time coming up with a rigorous philosophic activity to come up with a reforming definition, not simply a stipulative one, but one that is better than and will replace all the ones that came before it, that will take a bit of time, but you [don’t] have to be upset with that. You can be satisfied with what is here and spend your

time saying how does what we know about these definitions help us understand the scope of research that we want to put under the tent, meaning the tent of regulation or oversight or IRB review.

I do not know if that is helpful.

DR. BRITO: No, that is very helpful and I agree with that and I think that is my point somehow in all that is that the description within the text is much more clearer than the actual recommendation -- and it leaves less room for interpretation.

PROFESSOR CHARO: I think actually that also then very nicely leads to some -- a game plan for what to do next because it may make sense to leave the first paragraph of 2.4 the way -- to abandon it for the moment and instead to say something like human participant research has the following characteristics. It involves humans. It involves an intervention or a something or other.

Kind of make a list, right, that is drawn from that and drawn from here, and then as we get through that list and work on the list, we can then begin to identify those things that will now be subject to federal regulation and, indeed, it offers us a chance to identify why they should.

Finally we will be able to have a place where it says it is -- although there might be benefit to the individual participants it is primarily for a different purpose and finally we will get a chance to say why it is that comparing two standard treatments against one another should be considered research because that is an enduring challenge from the clinicians out

there and we can also list the reasons why certain things are being exempted or whatever phrase we turn out, and then we will come back after we have made such a list to try it out again and see if it works.

The subsection in 2.4 in which human participants are defined, we already know has a discussible issue within it. Why don't we just start first just sentence by sentence just to see which ones we can live with comfortably and then focus on the ones that need discussion.

The first sentence says that they are live-born currently living individuals, whose data are being collected or analyzed or being exposed to manipulation. It incorporates the notion of live-born currently living individuals as human participants, right, and it has the functions as the text says of excluding embryos and fetuses because they are not live-born and excluding the dead as a class. Right. So are we comfortable with that just to start with that?

DR. BRITO: No.

PROFESSOR CHARO: Okay. Arturo?

DR. BRITO: The fetuses, I have a hard time with that, and so I was looking for the text. I forget where it is mentioned in there. I think there are some -- I have some difficult issues there.

PROFESSOR CHARO: All right.

DR. BRITO: Because -- I have to put it all together -- I am concerned about loop holes here, which could -- the embryo

part, you know, working with the last report, I worked through some of those but the live-born or fetuses are not to be considered live-born, I have some difficult issues with that.

PROFESSOR CHARO: Let me just ask, if I may, just to understand then what we do with that. Are you looking for an incorporation of fetuses into the notion of human participants so that the rules that we are writing generally here would also apply to fetuses as a whole or are you looking for what the text had suggested, which was a stand alone set of rules that identify fetuses as research subjects? I think participant is probably a foolish word under those circumstances. Research subjects under such circumstances. And here are the rules that will govern. Many of which may be the same as covering other research but some may differ, et cetera.

I mean, which approach is it that you are looking at?

DR. BRITO: The latter. I feel more comfortable in the text. The problem with these recommendations when they stand alone and what happens is that -- just like, you know, you take the Common Rule, if you just look at the regulation in isolation of the rule and people take whatever interpretation -- I should not say one -- however they interpret.

You know, there are 100 different ways to interpret a lot of these regulations and that is what my fear is here because the text describes it nicely and goes on to say -- I cannot remember if it is Chapter 3 or 2 -- but how there are other regulations for this. So that I am comfortable with.

I am uncomfortable here with not including some --

PROFESSOR CHARO: Some acknowledgement of that?

DR. BRITO: Right. In the recommendations.

PROFESSOR CHARO: Okay. Marjorie, that can be handled somehow in the drafting of the rec so that we can highlight that fetal subjects or fetuses as subjects of research is addressed elsewhere. Right?

Bill?

MR. OLDAKER: I do not disagree. I just have a question. Is there a difference between the mother as a human participant and the fetus as a human participant?

DR. BRITO: You mean a difference in the way it is described?

MR. OLDAKER: I am just wondering if it -- intellectually if we are making a distinction.

DR. BRITO: I think the distinction is made in there. Is that not correct? If I remember correctly the way it is described, the distinction is made between the mother and the fetus as two separate, participant and subject.

DR. SPEERS: Right. And currently in the regulations, in the Subpart B of the regulations there is a difference between pregnant women and fetuses.

DR. MURRAY: Just to reinforce what has been said, I think if we use this particular formulation of live-born, it would be perceived by some parties as a stepping back from providing protection to fetuses who might, in fact, be born as children and

I think that would be an unfortunate message because I do not think --

PROFESSOR CHARO: Would it make sense instead of defining human participants as live-born from the living, say simply that these regulations apply to live-born currently living human participants and that allows one to not say whether or not fetuses are considered to be human participants or not. Simply that these regulations do not apply to them. There will be different rules that apply to them. Is that somehow a way to capture your point or is there -- Larry and Bernie and Trish?

DR. MIIKE: I think we should just -- we keep this but drop "live-born" and you can say that other regulations are in place and we support there being a case for embryos because it does not -- these -- the regulations -- I mean, the system we propose here does not make sense to have the fetus or the embryo as the participant. How are they going to give consent?

You know, all of those kinds of issues arise and so rather than raise it to the level of people attacking this by saying things like live-born, et cetera, simply have a footnote or something attached there that says on the issue of the embryo we are keeping that as separate because these kinds of regulations do not apply to that situation but there are regulations in place in protecting the embryo.

DR. MURRAY: So, Larry, would you strike "are live-born currently" and just go to "living'?

DR. MIIKE: I would just say "human participants" refer

to living individuals.

DR. MURRAY: Good.

PROFESSOR CHARO: It begs the question of the definition of living though, which gets us into a more --

(Simultaneous discussion.)

PROFESSOR CHARO: In some ways live-born is less controversial.

DR. MIIKE: You can either footnote it or refer that we understand that there is a controversy over whether the embryo is a person. The current regs have a separate section for protection of embryos, et cetera, and that -- and then if you have to go into more explanation you can say why this system that we are setting up is not really apropos for an embryo versus someone who can speak for themselves or have a guardian who can speak for them, et cetera.

PROFESSOR CHARO: Trish and Bernie?

PROFESSOR BACKLAR: Well, I agree with Larry. I was going to suggest that we take out the "live-born." Delete the "live-born."

PROFESSOR CHARO: Bernie?

DR. LO: Yes. I just think this is one of the situations where we need to be prudent rather than precise. I mean, there are currently in place very sort of carefully crafted regulations on fetuses and anything that looks like we are sort of backing away from that is just going to cause trouble that we are not meaning to cause.

I think we also have to be careful that -- as Arturo was saying -- I think the issue is not -- there obviously are debates over embryos as well but the real concerns I think really are with fetuses, especially fetuses approaching term or having viability.

And I think, you know, that sort of sharp line between, you know, what is a person and what is not gets blurry to some people there and we need to not fight a battle that has already been fought and decided and to just, you know, say that we are going to adopt or that we support the maintenance of the current Subpart B.

DR. BRITO: I was going to say I was looking for the language here that is, in fact, before the recommendation. It is actually after on pages 29 and 30. Just one quick sentence basically at the top of page 30, line one. That pretty much satisfies -- it may need a little more elaboration here.

PROFESSOR CHARO: Well, at a certain point then it makes no sense to try to define human participant. It seems like it is self-defined and then one simply writes a series of exceptions. Notwithstanding the above, these regulations do not apply in their totality to the following classes: Embryos, fetuses, the deceased.

DR. BRITO: Which are protected by other --

PROFESSOR CHARO: Which are covered under X, Y and Z. Right? And then that way one gets away entirely from the definition because at that point there is nothing left in the

definition except the stuff that is the hot button stuff like what constitutes living.

Bernie?

DR. LO: There are two other issues I think we may want to address. One is the family members of --

PROFESSOR CHARO: Yes, we are going to get to that.

DR. LO: And the second is there are also situations in which, for example, in health services research health care workers may, in fact, be the subjects of research in the sense that they are put at risk. That if you are score carding people and keeping track of who does a better job, the -- even -- you are primarily collecting data about the patients who are receiving care in a system but if you are going to analyze it by hospital, by physician, by physician group, in fact that has a lot of implications in terms of risk and benefit for those people.

And to what extent -- I mean, there are two issues. One, to what extent are the risks and benefits to those individuals who are not classically thought of as research subjects to be taken into account and then there is the issue of consent.

PROFESSOR CHARO: What you need then is a definition of participant, not a definition of human, right? Participants are those about whom data are collected, analyzed, et cetera, and you drop out the human to get rid of the hot button because that would answer your --

DR. LO: Then we need to think through -- I mean, the

risks and benefit assessment, and then the consent issue becomes really dicey there. If you are doing quality improvement and you have to get consent from the doctors, it is not -- it is impractical in some sense but not in the senses that it is commonly used. You could do it but, you know, they just will not cooperate and that is not impracticability. They are refusing.

PROFESSOR CHARO: Bill?

MR. OLDAKER: I think, you know, if the definition were limited to human participants are living individuals and then you do your exception, I think it probably accomplishes it. I think that it is important to exclude cadavers and cadaver material. I mean, which historically has been. And I think if you do it the way you were talking about, I think that would deal with that issue.

PROFESSOR CHARO: All right. So clearly we have got to find a politically sensible and sensitive way of flagging the fact that this proposal does not apply to fetuses and embryos without necessarily wading into the substantive debate about how to characterize fetuses and embryos.

The next item, as Bernie has anticipated, is in the next sentence. "When data are obtained, it is through intervention or interaction with the individual..." da, da, da "Living family members are human participants...when data are collected or analyzed about deceased individuals where the consequence may be risk to the living family members." Larry?

DR. MIIKE: No.

PROFESSOR CHARO: Bernie?

DR. LO: I mean, the first is this -- you can also have concerns even if the subjects are alive rather than dead should you count family members as being affected in research. And then there is the people who are not biologically related to the subject of the research but who as in the care giver example I threw out have an interest in research because they may be put at risk.

DR. SPEERS: If I may --

PROFESSOR CHARO: Please.

DR. SPEERS: What we could do with this piece, this actually builds from the discussion in the HBM report and all I was going to say is we could go back to the language if you want that is in the HBM report where it is a suggestion for investigators and IRBs to take this into account.

DR. LO: Marjorie, maybe I am misinterpreting the placement of it in here. I read this to say that living family members of humans in research are human participants in research. Therefore, we are going to treat the family members, even of people who are deceased if we are going to handle their tissue, just like if I were enrolled in a clinical trial. And I am totally against that. I think we already addressed that in Recommendation 3.1, which is to direct IRBs to be concerned about impacts on community and other related individuals, which is consistent with the HBM report.

But tell me if I am wrong by including it in this

definition here. All of a sudden they become the human subjects for which all of this system has to be satisfied.

DR. SPEERS: Let me just give you -- to answer that, let me give you just a practical answer in terms of how IRBs sometimes make determinations about whether they are looking at a project that involves human participants research, which is they -- a determination will be made of whether it is research or not according to the current definition of research, then they have to make a determination of whether human participants are involved.

The way the regulations are written now, deceased individuals are not human participants. So that research automatically is kicked out of the system. It would not get reviewed unless an IRB on its own says wait a minute, these are deceased individuals but there are implications for the family members.

So the question is whether -- I think the issue for you is whether you -- whether in these kinds of studies if we put some qualifiers on them, whether you want those to be -- to fit under the definition of a participant or not fit under that definition because what will happen practically is some IRBs will review them perhaps and some will not.

DR. MURRAY: I will try to think of a case again. I just imagined one. A hypothetical individual dies of a rare tumor. They take -- a scientist takes the tissues, determine that there is a very interesting mutation, a lethal mutation. The individual on whom the studies being conducted being dead does not

count as a human subject. Therefore, the confidentiality -- identifiability is not an issue. They can be identified in all of this. And so what would stop a scientist, other than common sense and decency, from publishing this study identifying the person by name and saying all first degree relatives have a 50/50 likelihood of dying horrible deaths from this same mutation?

I guess the question is, is there -- (a) is it worth trying to catch those kinds of cases in our definition or not and (b), if so, how are we going to do it?

DR. SPEERS: Let me give you a real example. Not a hypothetical one but one that I have dealt with and I have shared this one with Bill Oldaker before.

This was a study where an individual had died an unexplained death and so they wanted to examine the tissue from that individual and if -- and they wanted to test the tissue for HIV. If this person was HIV positive then they wanted to go to the person's spouse and tell her in this case that her husband had been HIV positive and test her as well and then try to, you know, study what the risk factors were.

So in that particular case we all determined that that was research and that in that case the living individual was a participant because there were potential consequences for that person. She was going to learn potentially something about her husband that may not have been implications for her as well.

DR. LO: Marjorie, in your example did it become research when you went back to contact the spouse and say we want

to now get information about you and a blood sample? If they just said all we are going to do is an epidemiologic study of undiagnosed HIV in deaths in a certain population --

DR. SPEERS: It was research. It was research before this particular case came up. There is a standing research study to look at possible explanations for unexplained deaths. And normally the participant is -- normally it is the deceased person that is the -- but sometimes there are family members.

PROFESSOR CHARO: Larry?

DR. MIIKE: Can I ask a question? I can understand the reasoning behind what you have just said and the concern for the living family members but what I am concerned about is -- and you can answer this question -- by placing it in here in such a research, would that then have been imperative that the wife be asked for permission to conduct this research even on only the tissue -- the remaining blood sample of her deceased spouse even if they had no idea -- they had no intention of linking it to her?

DR. SPEERS: Well, the way that I would prefer to answer that question is that having the definition of research and pulling something in for the IRB to make a determination of whether it is research or not research or the type of review it has, does not speak directly to whether you have to directly obtain consent. So, I mean, I would say you have to look at the additional factors and exactly what their plan -- you know, what they are planning to do in the study.

DR. MIIKE: My second question along this line is that

why first degree family members? Because if we are talking about genetic studies, it is quite plausible that second and third cousins would be affected by certain markers, et cetera. So where do we draw the line on this? I just find us going into a morass in this.

PROFESSOR CHARO: Bill?

MR. OLDAKER: Marjorie knows that my problem with this is the unexpected consequences from it. We know right now that, you know, from various cancer research centers that many, if not all of the tumors are being basically dissected and put into basically computer run models. And, you know, that is being done almost as a matter of course.

And if we create rights for the deceased, which they currently do not have, I think that we going to create complications in the research to make it much more difficult which is not our intent, I understand. And I understand our intent is to protect people who, as you point out, could be -- have their rights inferred.

I think there is a different way to go at it. I think that as Bernie, I think, was suggesting, the wife would become a subject once they go and ask her to obtain her blood sample. It is not -- and that in and of itself is, I think, enough to make her a human participant.

I think trying to cover it through the deceased individual who basically under our laws has no coverage for anything at the current time, they are not recognized as a human

being. To try and put them under it creates an artificial definition which I think we will find will cause us many more problems than we can foresee.

PROFESSOR CHARO: Jim?

DR. CHILDRESS: So I guess what we are after here is to get this in under research in some way for review. Right, Marjorie? And then we do not need to get family members in any way other than we did in the human biological materials report and talking about the impact on those individuals would be something we would have to consider.

But the real question is whether we get it in for the kind of review we think is appropriate.

And I guess I am not as convinced that the dead have no interest or rights in the extreme language of this particular document because there are many ways individuals, while alive, can control their families and have an interest in what happens to their bodies after death. So I think we are a little too cavalier here in simply thinking that there are no interests, for example, in reputation and a whole host of things associated with that.

So I would urge us actually in the text to downplay that a bit, which just as another way to open the question is to -- given what we have said in the Human Biological Materials report about tissue, what ways do we have there to bring this under review that would permit us to do what we want to do here without doing it all through the language of human participants?

MR. OLDAKER: I would have much less problem if we did

it that way because I think then you get around the issue of granting rights to -- I mean, if Larry is right, the third or fourth generation of people could come in and make objection, what you really want to do is you want to facilitate the research and there is no doubt that people in life can determine whether they want their tissue after they die to be used and not used in various ways. But usually at that point in time the rights of the second parties does not exist.

PROFESSOR CHARO: Trish, and then I have got Eric and Bernie.

PROFESSOR BACKLAR: I want to ask a question because I cannot remember precisely how we dealt with this issue of getting information and the kind of story that Tom told of genetic information that would give you information about somebody perhaps who died young but yet potentially was going to have Alzheimer's and you could find a trait in other family members. They want to know about it and they want to be contacted or they may not wish to be. How did we deal with that precisely in the Human Biological Material?

DR. MIIKE: In a prospective way that was under the control of a subject, him or herself.

PROFESSOR BACKLAR: Okay.

DR. MIIKE: It was not to let the family members in on that decision. Of course, we still face the -- we could design a prospective system so that they could only do follow-up research that was agreed do by the living subject. But we are still faced

with the dilemma about the existing tissue samples.

PROFESSOR BACKLAR: Right. So I would want us to echo that here if that is possible.

PROFESSOR CHARO: Well, in the HBM report we said that you could use tissues from deceased persons, current stored tissues from deceased persons.

PROFESSOR BACKLAR: Right.

PROFESSOR CHARO: Without needing any permission from anybody else even if that tissue had the potential to reveal information that could ultimately cast some light on currently living relatives. We just are stuck with the current rules regarding the treatment of the deceased as nonhuman subjects and not subject to federal regulations.

PROFESSOR BACKLAR: But there was the prospective.

PROFESSOR CHARO: Yes.

PROFESSOR BACKLAR: From now on in. So why can't we get consent?

PROFESSOR CHARO: That would suggest that unless people enact some kind of written document that says you can do research on my tissue after I am dead, the tissue is not available and that would be a tremendous change in the presumption. We could certainly write one where people are allowed to write documents saying you may not work on my tissue, which would be far less of a loss to epidemiological research. But to require it before tissues from the dead could be used would have a profound affect I would suspect on epi work in the U.S.

Bernie?

DR. LO: I have a concern that we are spending a lot of attention on a relatively minor point compared to a lot of other things. So we have a definition of research that is flawed in both directions. Earlier this afternoon we talked about how it swept in things that we want to kind of quickly get out from under the definition.

Now we are saying our definition of research may be flawed because there are some studies out there on deceased people where we still have concerns enough that we would like the IRB to be able to take a look at and now investigators say, no, you cannot touch me because this is not research, nani-nani-nani.

(Laughter.)

DR. LO: So I think we just need to say that. You know, there is some -- as Tom said, you know, there are some situations where it is not technically in the regulations but common sense and decency would mean you ought to let someone look at it just to make sure that you are not trampling on the interests of people who are not technically subjects but have the possibility of being harmed.

But not try to tinker with the definition because then we just -- it is like a Rube Goldberg issue where you tinker with one thing and then you have all these other downstream things you have to worry about. I just think this is not -- this is not the pressing reason why we are being asked for oversight of human subjects. The dead people are rising up and saying, you know, you

are not protecting us.

(Laughter.)

PROFESSOR CHARO: So you want investigators to have a kind of personal code of ethics that would go beyond the requirements of law?

DR. LO: In certain circumstances we can say even though this does not technically fall under the federal regulations, we want you to come in and let's talk about this thing you are proposing.

PROFESSOR CHARO: Eric Meslin and then Bill Oldaker?

DR. MESLIN: My point may be unnecessary now. I was just going to remind the commissioners what you said in the HBM report and the way you dealt with was virtually the same way that Bernie has just described it by drawing attention to the interests that the deceased might have as reflected through their family members.

Alan Buchanan's commissioned paper went into great detail about this and people were quite moved by the paper, although he did not give a lengthy exposition of it at the Portland meeting. But the paper and the points in that paper were adopted in spirit if not in text. And it is -- the recommendation that you adopted in the HBM speaks to this issue in the way that Bernie has, which is you have got to be thinking about these things even though for purposes of federal regulation the deceased are not human subjects. That is not the point. The point is a more nuanced and subtle one.

I was going to -- when I originally put my hand up for Alta, I was really going to ask Jim to tell us exactly what he meant, not right at this moment but perhaps afterwards, about either toning down or being less cavalier because we will obviously want to do that if what I have just described about the Buchanan work is what you were referring to.

DR. MIIKE: You cannot be less cavalier.

(Simultaneous discussion.)

PROFESSOR CHARO: I have Bill, Diane and Tom on my list.

MR. OLDAKER: I will try and be quick. If, as Eric says and Bernie says that they are not covered as human participants but they are covered as an ethical responsibility to look at, I think that makes a difference. I just worry that definitions have the ability to become kind of legal precedents that will go beyond what we really intend to do. So that is fine. As you say, Eric, I can live with that.

PROFESSOR CHARO: Diane?

DR. SCOTT-JONES: I just want to ask a question to clarify something that Tom and I were talking about outside the main conversation. I was trying to figure out why we put the second statement in here and is it the case that once somebody dies that say whoever is around when they die can use their tissues? Is that why we have that in there? What is the current law? I just do not know. I am asking.

PROFESSOR CHARO: The body -- the cadavers are the

subject of great debate in terms of their status and property of whom if property at all. But basically next of kin have dispositional authority except for certain public health purposes like how you bury somebody or how you cremate somebody.

But once there is tissue that is archived, then researchers who want to use the tissue can use it without being subject to the federal rules we now have. That means that they do not have to go to an IRB first with a protocol and a plan. They can just use the tissues however they want.

That is not to say that they can get access to the tissue without having to ask permission from somebody else. They probably have to ask permission from whoever owns the archive.

In some states they may have to go to the relatives. I think that would be very usual but as a matter of state law you would have variations on the degree to which relatives continue to have control. All right.

And in some areas, for example, we have seen with Native Americans you may have to get permission from descendants many, many years later than the death took place because of a notion of a kind of collective quasi-property interest in the remains.

So it is not as if the researchers can just go in and body snatch. It is really about whether or not they have to be subject to the federal regs that include things like review by an independent group.

Tom?

DR. MURRAY: This is not a point of great significance

but I cannot resist making it. Anyway, I thought Bernie's comment was very wise. This is -- of all the things we have got to worry about -- not the most significant probably.

And his notion of his image of the dead rising up to exercise their -- give us their opinions, just leads me to suggest that we denote this as the Dr. Bernie Lo Halloween clause.

(Laughter.)

PROFESSOR CHARO: I sense that we are beginning to lose it.

(Laughter.)

PROFESSOR CHARO: And although we have 27 minutes which we could devote to Chapter 4, it might be better to devote that to rest and relaxation, and maybe some progress towards some redrafting in anticipation of tomorrow's review of where we have been today.

So I would suggest if there is no objection that we adjourn until tomorrow morning and we will begin fresh with Chapter 4. Thank you for a very productive day.

(Whereupon, at 4:35 p.m., the proceedings were recessed.)

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