47th 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

OPENING REMARKS

HAROLD T. SHAPIRO, Ph.D.

DR. SHAPIRO: Colleagues, I would like to get our meeting underway, please. I would like to call the meeting to order, please.

Before we get to the principle item of business before us, which of course is our -- the draft report and issues that surround that, let me turn to Eric who will give you a brief update on other matters on the commission's agenda.

OVERVIEW OF WORK TO DATE

DR. MESLIN: First, I want to thank Marjorie for suggesting Atlanta and to welcome everyone to Atlanta.

You have a number of handouts, and the public also will have them. A quick update for those who are interested about our International Report. It is at the editors and we expect that it will be available and on our website in the early part of April and then a hard copy available in May so I did want to point that out.

And also take this opportunity to thank Alice Page, who all of you know has worked so hard on this report and other staff. But I know that you will all

join me in thanking Alice for her tireless effort on that report.

There are also a number of handouts that Ellen Gadbois produces in terms of the legislative updates and if you have any questions about those please let us know. Those indicate to you, I think, how interested Congress is and others in what not only NBAC is doing but in the areas that the commission is interested in.

I have no other dramatic statements or even boring statements to make at this point. Mr. Chairman, I will leave those to your colleagues.

ETHICAL AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS

DR. SHAPIRO: Well, thank you for restraining yourself and maybe we could all follow that example.

Let me address -- begin our discussion with respect to the draft report that is in front of us and I want to suggest a reorganization of the agenda if the commission does not object and let me try to tell you what I have in mind.

First of all, I want to thank Bernie for that detailed set of comments that he sent around. I really appreciate the thoughtfulness of those remarks and in my own case as I tried to go through each of them

carefully and go back to the text and consider what my own thinking was along the lines, a number of issues came to my mind, which I thought we really had not addressed appropriately and need to come back and talk about in a substantive sense.

I want to raise some of those issues in a minute so I have two or three broad issues, which I would like to get some commission discussion on in that respect and so I would like to do that before we start going through things point by point.

There are also other commissioners who have some issues that they want us to discuss and I think at least the ones that I know about are quite appropriate, that is things that we need to be a little more clear about. Some of them have to do with the nature of the report and the way it is written and how it is organized. Others have to do with very substantive issues regarding who it is that is a participant and is our definition of that really correct or should we rethink that and so on.

So I would like to go to some of those issues before we start just going through the report recommendation by recommendation. And I will let, of course, commissioners speak for themselves. I mean, a number of them have spoken to me about issues that are

of concern to them. I do not want to try to summarize those, although I think I understand them. I want -- I think it is much more helpful if commissioners speak to those issues themselves.

So if it is all right with you, I would like to spend some -- whatever time is necessary to clear these things up or at least identify them and see how we think about them. I do not know about clearing up. We will have to see what the issues are and how easily they are cleared up.

Now I do not think we should feel -- despite the e-mail I sent to you, I do not think that we should feel any unnecessary pressure regarding having to sign off or complete and so on. I mean, I do feel some time pressure to be honest with you. I think we ought to get on with this and -- but whether we do it this month or next month is not a big huge deal.

After all, it is not some event that we are trying to deal with here. We want to get it as right as we can. I do not think we have the luxury of a very long time horizon of this report but it would be artificial to say we have to do it today so I do not want to really focus our attention around getting that much done today or tomorrow. Perhaps we will and perhaps we will not. And perhaps we have a meeting at

least tentatively scheduled roughly a month from now, which I think is April the 17th or 18th, something like that, back in Washington. And so that is available to us and maybe that will be the time when we feel we feel good enough about it to say, okay, let's go into a somewhat different mode.

So I just do not think we ought to, you know, bind ourselves to do that today because in view of what some of the issues that have come up at least that I have thought about and others have thought about, I think that might be a little unrealistic but we will get as far as we can.

We will have a quorum of course tomorrow morning. Not all of you will be here tomorrow morning but we will have a quorum and we will meet tomorrow morning. My guess is that we will adjourn some time after 11:00 tomorrow morning and before 11:30, simply some time after 11:00, rather than 12:00 o'clock just given the logistics and the flights that people have to make. That seems to be what is realistic.

So if you do not have any objection to that we will just go ahead and deal with these issues as they have been identified.

Now it is hard to know which ones to deal with first but why don't -- Alta, if you do not object, why

don't I turn to you and summarize -- ask you to summarize for the commission the number of issues that we have been discussing this morning regarding the nature of the way this report is structured and what might in your judgment be a better way to proceed if I have not misstated your concern.

PROFESSOR CHARO: No, that is fine. There are a lot of people here who I have had a chance to talk with anyway so it will not come as a surprise but following Bernie's e-mail last week in which, among other things, he expressed a concern about alienating some people who might otherwise be supportive of efforts in this area because of their disagreement with specific details about implementation that would be recommended in this report, I found myself recognizing something that I should -- I think probably we have all noticed but did not articulate to ourselves. And that is that the recommendations, and as Trish noted in the taxi on the way in, the text as well tend to merge the goals and the proposed form of implementation for reaching those goals. And the merger is so complete that at times it is difficult to actually clearly identify the goals that we want to achieve in terms of a system, for example, that is uniform, that is comprehensive, that is flexible, that is adapted to

varieties of kinds of research that endorses a decentralized focus in which the main repository of responsibility and discretion for ethical conduct of research lies in the hands of the investigators and the boards that assist them rather than in the government -- a goal of having the government's role being one of facilitating investigators and boards in that job through education, through guidance, through mechanisms that facilitate collaborative research in a way that is efficient and effective. And that to some extent this was either getting obscured because of the merger with details about implementation or at times was not even being said as explicitly at all as it should be.

And so my initial reaction had been to suggest that the recommendations be rewritten so that there be one list that simply says these are our goals and another that says these are the ways that we have to date seen for implementation, others might see a different way of doing it.

And then, as I mentioned,Trish said, "Well, you know, it makes sense to do the same thing with the text."

From that conversation and then a dinner conversation with Bette and Alex, and then this morning what emerged -- and then with Eric last night, what

emerged was the possibility of creating a very short, very punchy and very pungent separate document, which would stand in relation to this larger document in a way that we have not quite figured out yet but would be very much separate, could be read on its own, that would be entirely focused on the goals. Something that might have somewhere between 10 and 15 or 10 and 20 items listed as the focus of our efforts. In some cases it is affirming something about the current system. In other cases it is a change. We affirm the decentralized focus.

We want to make changes with respect to things like we believe that it is time to move away from a notion of categories of vulnerability in which certain people are constantly viewed as vulnerable and move towards a more contextualized view of vulnerability in which we have simply asked for these participants in this research are there any special issues about inability to protect one's self that should be addressed in which we focus on notions of risk and what would be new.

We affirm the notion that a risk/benefit balance is what needs to be done. What is new is that we would like to clearly identify or clearly state the notion that we have to be looking at risk for each

element of the research and that an unduly risky element can be justified by the existence of some other element elsewhere in the research that is in and of itself potentially beneficial.

And by doing this separately we make it very clear to people where we are headed. We have two to five paragraphs following each one that explains, if need be, what is in that. And we cross reference to this other document and say now one -- the way that we have seen so far to implement this is represented in this document at text, pages such and such, and recommendation such and such. And it leaves room for the possibility that as members of the executive and legislative branches take advantage of this report that they might see other ways to implement that would work better or be easier to pass or be easier to administer.

But each change they make from the kinds of things we recommended, it would ask them to justify it by saying how will this further the goals equally well.

So in a sense what I am suggesting is, God help us, a new document but one that is very short and very much to the point.

DR. SHAPIRO: Let me just make a few comments about that and then just open it up for discussion.

Others may want to contribute.

I think the diagnosis or the observation that I believe Alta made -- I hope I am not misreading or misunderstanding -- that the current document that we have, which is very comprehensive and very detailed, indeed, does have the efficiency, if I understand it, of sort of merging goals and procedures together such that the goals often get lost and I think, you know, on reflection, although I did not think about it in that way to be honest, on reflection I think that is an accurate diagnosis.

And having something -- and I do not know what the exact structure should be, that is not that critical right at this minute but it seems to me that the benefit of attempting something like that is that implementation, the exact way goals are implemented are always going to be up for discussion, right, because you are making -- there are empirical issues which you cannot really resolve until they actually get tried out there. You know, is it going to be more bureaucracy than the protections are worth? Some of those issues just cannot be resolved until something is actually tried and so it gives us a chance to think of the implementing recommendations and some sense in a more modest sense.

We do not have to say this is the way to do it. We can say here is our ideas regarding how it might be done and it leaves open the possibility for others at some other time as a result of experience to say, okay, we can stick with these goals but, you know, life has turned out such that these ways of implementing it are either useful or not useful and so on.

So it has that characteristic, I think, and so the general idea of doing something which make clear what our goals and commitments are and what we are trying to achieve, and then look at the implementation as a somewhat separate issue sounds attractive to me.

And, again, we would have to work it out. I do not know what the exact structure should be but let's see what others think.

Alex?

PROFESSOR CAPRON: A couple of comments. First, I endorse the vision that Alta has put forward. Secondly, I think I would like to be clear that we are not talking about something which is the equivalent of our so-called executive summaries.

DR. SHAPIRO: Right.

PROFESSOR CAPRON: We really are talking about a report of 10 or 15 pages that is vision -- a vision

of how to respond to identify problems.

The third point there is an interesting comment that Ellen Gadbois mentioned at breakfast this morning, which is that the staff already has and uses in presentations around Washington a document that has roughly 10 problem areas identified, followed by the NBAC response.

And obviously -- since I agree with Alta -- the chapter we are talking about or the part of the report that we are talking about, the responses would be described in the type of thing that needs to be done rather than the detailed regulation but that still seems as though the structure or a potential structure from which one could write relatively quickly -- I always think about these things having sat where Eric is now before -- how do you get this done. And it seems to me that if we had that and if that could be retrieved from Washington today for us, it might provide a means of making sure that we are all -- that we know what the next thing is going to look like because the worst thing would be to come in April and have a document which does not do what we have just said we want to have done.

The final point is I do not think that we should see the part that is more specific as an

appendix. It is rather part two of a report but I very much agree with your comments, Harold, that we are not the advisory committee to the Office of Human Research Protections, much less to the not yet created National Office of Human Research Oversight.

If we were, then actually going over the language of regulations would be appropriate, but we are not so the most we can hope is whoever drafts them buys into our vision and maybe gets some guidance if we can give a good rationale for one solution or another on how to achieve that vision.

But we are not going to control them by writing more detailed recommendations. I mean, we just do not have that power. We will not be around to start off with but no one will feel compelled and there will be a lot of struggle back and forth among the different actors over the language of those recommendations in the end.

So being more detailed about it, unfortunately -- even if we had strong views about the way it should be -- will not achieve that. So it is kind of butting our heads against a wall on that point. So I think that what Alta describes is very attractive.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: I think using the materials

that the staff has prepared is an excellent idea. I would want to -- until we have actually gotten a chance to look at them it is going to be hard to know exactly how close they are but I would not want to suggest that we think of this document as something that is truly de novo. That -- anything that is given to us as a resource but not a first draft.

I also think that this may be the kind of document for which commissioner input and commissioner writing may be very, very important because in the end it is people like me coming in the night before the meeting saying, "Uh-uh, this is not what I want." That can derail the whole schedule. So the only solution is to actually do it ourselves so that we cannot --

PROFESSOR CAPRON: I think you just volunteered.

PROFESSOR CHARO: Well, I said ourselves. Because --

DR. SHAPIRO: Maybe we will do some writing today. We will see how things go but chances are we will -- I mean, not that we can complete everything but I think we have to address the issue.

Now let me just ask the commission if just -- again we are not talking about the details here. We have nothing to look at. It is the question of an

idea that we ought to have along with the material that we have here a short document, whether it is ten pages or 15 or 18. As we get to 20 it looks like too much but anyway it is going to be a relatively short document. That talks either about the goals that we are trying to achieve and are trying to achieve with this or, as Alex has said, you know, a vision of how to respond to identify problems because the problems are identified and they are listed out in our report quite accurately, I think, and so on.

But does that general idea seem sensible to members of the commission? Because if it does, we will immediately begin thinking about it.

Yes, Larry?

DR. MIIKE: Well, you sort of know what my response is going to be.

DR. SHAPIRO: Yes, let's get on with it.

(Laughter.)

DR. MIIKE: We are back again to our usual mode of when we get to the end of a report we all agonize and want to change everything again. And so I just really protest against that kind of an approach. I am really tired of the way we deal with these issues every time a report comes out.

Now if we -- I do not have an objection to a

shorter document but if the shorter document is in disjoint with our main report then it is going to be a very weird report that we are going to be putting out. So I -- it remains to be seen about what that summation is.

The other thing is that having read Ellen's stuff, I do not want a tone of defensiveness in our report that says, oh, you know, we are not into regulation, folks. No, that is not what we really mean. I do not want that kind of an attitude in the kinds of documents that we do.

And then to also say that if you are trying to predict how people react to our documents, I do not care how you write it as long as you get the main ideas of what we want out there. That is the main point. We cannot control how it will be used. So to try to tease out the policy aspects from the implementation aspects, to me is -- it is putting in an amount of effort that is not worth what the result is going to be.

Now I know I am not -- I am going to lose on this issue but I just wanted to say again that this to me is just the usual mode we go through and we just waste time and I do not think the effort is worth it but I think it is a fait accompli already. You people have discussed it and I think that is what is going to

happen.

DR. SHAPIRO: Rhetaugh?

DR. DUMAS: I can appreciate Larry's point of view because I have gone through that conflict myself about whether we are ever going to get a report finished.

On the other hand, I have had this feeling of uneasiness about the length and the detail of the recommendations so I am relieved by the possibility of doing something about that.

Whether we write a new document or whether we separate out maybe the goal of the recommendation from the suggestions for implementation in that same document, I do not think would matter very much to me. But I do think that it is important to do something about the recommendations because, first of all, they are very lengthy and they are very detailed. And as was mentioned, the major objective gets lost.

DR. SHAPIRO: David?

DR. COX: So I, too, really can empathize with Larry's point of view but I would like to just put an empiric test that I recently did on the table, which puts me in favor of trying to clarify what our goals are.

I just finished teaching with another

professor at Stanford the ethics course to the genetics graduate students and a group of 35 people who in the beginning did not want to be in the room and at the end were happy to be in the room but not because of this draft report but because of another shorter report that allowed them to be able to have a grounding to deal with all kinds of complicated ethical issues, and that is called the Belmont Report, because they were able to take that and use it as basic principles to work their way through many complicated issues.

And that as we tried to work our way through some of these issues, and I have not used this report as a grounding for them, but it was as an example on the web of something that we were, you know, dealing with. None of them could use it and they were all confused. So that is just an empiric data point and it puts me in favor of spending the time, although I do not know whether it is worthwhile or not, Larry, but at least I think that for me it would be helpful so that I will not get confused when I want to try and work my way through these things.

DR. SHAPIRO: Let me -- I am sorry. Steve?

MR. HOLTZMAN: So actually, Larry, I think that what is being suggested here is actually very different than the kind of perseveration we have

engaged in, in the past, because I think, like David's point about the Belmont Report, we started with some general principles and then really drilled down into the details to see where they took us and what was possible and what is not.

And I would not advocate dissecting and ripping apart the report. I think in that level and depth of complexity it is just fine. Now we are asking ourselves sort of in a final glory let's go back up now from that detail and say what was our over arching goals. All right. And lay that out succinctly in the form of something that looks and smells like a Belmont Report, and then maybe leave it to the lasting testimony that the general public will be able to -- whatever the general public is -- be able to appreciate.

So I think it is qualitatively different and I support it.

DR. SHAPIRO: Let me say a word about this, especially since the Belmont Report has been mentioned a number of times.

I think the report that we have in front of us is really very -- it is very detailed. It is very coherently written. It has a reality of its own and an attempt to take it apart would be extremely

unproductive. Now it can be improved in various parts in various ways and Bernie and others have had suggestions and we ought to try to incorporate those. And we have particular recommendations that certainly can be discussed and altered and changed in certain ways.

But I think it has a structure -- quite a viable structure and to attempt to take it apart, I think, would be extremely unwise and even we cannot really do it, would be equivalent to saying we are not going to write a report. So we have to sustain its own viability on its own.

And I think the addition of some material, some modest amount of material, which just reminds those who are reading through the details of the report of what our goals and objectives were and what our commitments were -- is -- could be very useful despite the fact that it is some extra work right now.

It is very different from the Belmont Report, however, in another way because the Belmont Report laid out a set of basic ethical principles upon which a system should operate and so on and that is why it has had so much life to it after all these years. I guess it is either 25 -- it is the 25th anniversary?

PROFESSOR CAPRON: 23.

DR. SHAPIRO: 23 years. The 20th anniversary we celebrated three years ago. Okay.

This -- the nature of this report is quite different in that sense. It does not take on the fundamental ethical principles. It asks how a system can be mobilized to achieve those principles. So it is different in that way. I just want to clarify that. It does not mean it is not useful or it will not be helpful because I support the idea.

And so I think we ought to attempt -- we will see what the results are. We will have to attempt to do it and if it seems reasonable to us, we can -- we can certainly think through how it will relate to this, what the pedagogical structure is and so on.

David?

DR. COX: Harold, I completely agree with that and so I would just like to extend it because when Alex was talking about specific examples, like ten or whatever the examples are, see I think that that is -- it is not exactly like the Belmont Report but it is analogous to the Belmont Report.

DR. SHAPIRO: I understand.

DR. COX: There is an analogy.

DR. SHAPIRO: I know.

DR. COX: So by then -- the analogy would be

those ten -- the practical issues that have been identified and what our principles are behind those. But you are right, it is certainly not a -- it is not an ethical foundation.

DR. SHAPIRO: All right. I do not want to take -- we will discuss during our first break, we will try to mobilize ourselves and see how we might actually implement something like that or at least give it a try. And then we will come back and see how to deal with it.

So if it is all right, we will go on to some other issues right now.

Yes, Marjorie?

DISCUSSION OF PUBLIC COMMENTS

DR. SPEERS: In the interest of group dynamics, I would like to comment on this proposal and say that I actually support it. I think it is a good idea because what we have done over the past year -- we started by asking some very basic questions about the oversight system and the scope of what it is we wanted to cover.

We have gone through that process and we had started with some things that were general and then made it more specific with more detail, and now that we have gone in it I can see now we have to come back out

of it essentially. And so I think that this notion of a separate document that outlines over arching principles and goals is actually a very good thing to do.

So I just wanted to say that so we can have a good day today and not worry about me sitting here --

DR. SHAPIRO: You will not dis-invite us to the --

(Laughter.)

DR. SHAPIRO: That is the most important thing we have accomplished so far.

DR. SPEERS: Right.

DR. SHAPIRO: Rachel?

DR. LEVINSON: I would also like to make a couple of observations from the perspective of a government agency, an executive branch agency receiving advice, that I have at times been frustrated with NBAC not -- sort of pulling away from giving detailed prescriptive implementation language and saying let's leave that to someone else when, in fact, you are the experts who might have language that would be very helpful that could move things along faster within the implementation phase.

But having said that, I would also say that when you do link up the goals and the implementation,

if the implementation plan is one that is not received well, there is the possibility and the danger of having the goal dismissed with an implementation plan that may be not feasible or not do-able or naive or whatever for whatever reason. So that there is certainly some wisdom in de-linking them in some fashion.

And the idea of a shorter document of some kind that outlines in a very succinct way the goals makes the rest of the report more accessible to people who are not going to go through a long report. Having the cross reference to the pages in the report that talk about implementation or talk about supporting text, again makes it that much more accessible. It is along the lines of what the OTA reports look like in their three versions. The one page, the ten page and the full report. But I would suggest not letting it go to anything more than 10 or 15 pages. Beyond that, it starts to lose its usefulness.

DR. SHAPIRO: Any other comments on this particular issue? Okay. Again, we will come back later on in the day with some ideas about how we should proceed.

Let me turn to some other issues which have come up that I have been told about and there may be others that commissioners have so I will go through

this list and we will go to others that commissioners might have before we turn to the report itself.

Bette, I am told by at least five people that you have a particular concern. I hope again I am not misstating it because it may be the sort of telephone tag idea and it may get mistranslated by the time I heard about it.

MS. KRAMER: No, not at all.

DR. SHAPIRO: Regarding the definition of participant and who we should consider a human participant for purposes of protection, and so on. So I would just like to hear directly from you and share with the commission what your concerns or ideas are.

MS. KRAMER: Thank you. I very much wanted to share. Last Thursday and Friday, VCU, you will all recall that a year or so ago, probably more than that, VCU had its entire research operation closed down by OHRP. It was OPRR at the time. Alleging that there were -- that they had -- that they had not handled the details of consent and other details around regulations -- around the regulations properly and that all of you that are involved with academic centers can imagine what a major blow that was to them.

At any rate, as a part of their negotiations with what became OHRP, to reopen their research they

were required to sponsor this two day conference on third party risk. And it took place last week and they had asked me if I would be the moderator, and it was really an outstanding two days. They had about 19 presenters representing ethicists, a lot of research scientists, two people who were prominent in the Genetic Alliance, who were the heads and founding persons and continue to be the chief person around groups focusing on particular genetic diseases.

They had people from the public. They had -- I said ethicists but anyway they had a broad spectrum of people there presenting.

Including the man, and I believe from OHRP, and I believe he was -- he is in charge of the compliance office. Is that right, Marjorie?

And anyway it was a highly charged conference because it was not a half hour old before OHRP was confronted with what turned out to be a really consensus feeling among the group and that is that they have created a new class of human subjects. And it was alleged that they have actually used the term "secondary subjects."

Now they said that they have not but there were people there who said that there is a long paper trail and they have actually, in fact, used it. They

did not really deny -- they did not deny that at least in their thinking that there is this class of people out there.

And what came across very, very clearly throughout the two days is that this has the -- this has the potential to really impede, if not close down, genetic research -- any research that depends on family histories. As soon as information or if information can be revealed about others then those others immediately become human subjects within this "de facto" class of secondary subjects.

So, for instance, in doing family histories, anything that they want to ask about families has got to be merged into one item. They can ask a general question about has anybody in your family ever had breast cancer, has anybody in your family ever had prostate cancer, has anybody in your family ever anything but they cannot become more specific than that. So it becomes -- it is very obvious that in terms of doing any kind of genetic research that is really meaningless.

If they have the identity of one person -- if they know a properly consented subject -- if a properly -- if they have the identity of that person's mother, if they have the name and address of her mother then

they have got to consent everybody in the family. As soon as one person is identified, everybody must be consented in order to be a person about whom they can solicit information.

Studies that exist, longitudinal studies where they have over the years collected identifying data so that they can go back, that they can go back and reflect whatever findings may come up or study more advanced questions or additional questions, they can no longer use because those people were never properly consented within this new perception of a class of secondary subjects.

You know, I do not think I need to say anything more. You can see how hamstrung they are. Marjorie was very, very helpful to me. We had multiple conversations before the conference when I was trying to -- I was trying to discern what it was that we were saying in this report that might be helpful. And despite all of her help and my going back and looking it over and looking it over, I felt that we are ambiguous in this. And I would like to bring it to the attention of the commission because I think it is vitally important. It is not just important to VCU. It is important to all the institutions.

And what they told me is that because

institutions are so frightened of having their research closed down that where it might be a proper matter for consideration of the IRBs, the IRBs are reflecting the concern of the institution running very, very scared and, therefore, being extremely conservative out of fright in what they have to say about the issues.

DR. SHAPIRO: Okay. Again thank you. That is very, very helpful, Bette. Very nicely articulated for us.

And, as I said before, this has to do with how one defines a human participant for purposes of this and we will go in a few moments to that part of the -- where that recommendation is. I have got all these numbers in my head and I cannot remember which one it was. But let's see -- I think people understand the issue.

Alex, you wanted to talk about this?

PROFESSOR CAPRON: I just wanted to respond. I think that besides the specific issue, which Bette has raised, it is one more reminder of the legacy of the biomedical model that has operated because I think that the view had been if you do research, the concern is risk to the person on whom you are doing research. And I was trying to think of in the biomedical model exceptions to that and I remember when we were working

out the points to consider in the Recombinant DNA Advisory Committee, we recognized that to the extent that a recombinant molecule was being injected in a person, if it was risk of infection, you had to be concerned with other people. We never defined them as subjects. We simply said the risk to them is one factor that the people designing the research and the people approving it have to think about and minimize.

When you get to all sorts of the genetic studies, and a lot of social science where what you are looking at is the individual situated either biologically or socially with other people who influence behavior or influence health status in one way or another, you clearly are going to end up with information about other people.

And I think that we really could say something useful about the ways in which the nonbiomedical model has to be thought about for the effects and why without calling someone a subject, you can be concerned about the risk to them and that if the research were creating an undue risk to those people, it would be a reason not to do it. It would also be a question of how the research is then designed so that this information is treated with greater attention to confidentiality even though in the strict sense there is not an

investigator-subject relationship there.

I mean, I do think it is different. I mean, I can give you any information about my family or anybody else I know and they have no protection from my doing it. If they have shared a confidence with me or if I just have information, I can share it. It might -- you might think me a bad person to do it but I can do it and then you can spread it around.

But if you are a researcher and I am giving it to you, I think some sense that my giving it to you is different than my just gossiping about it makes sense and so I think we can talk about the kinds of concerns that may have motivated people to say the notion of a secondary subject without creating the complications that would arise and that prevent the kind of research that we are describing.

DR. SHAPIRO: Larry?

DR. MIIKE: If I understand what you just described, Bette, and what we have in our report, the basic issue, I guess, is that we are saying that these are not human subjects of research but your IRBs are looking for guidance. And in our report I think all we say is that we basically punt to the IRBs and say in this situation they are not considered human subjects but the IRB should take a look at it. And I guess in

that sense our report is not helpful in this situation to the concerns that have arisen.

DR. SHAPIRO: Could I just -- Alta, and then I would like to ask a question about our actual recommendation. Alta?

PROFESSOR CHARO: It seems to me that ironically part of the problem here is in the language. I mean, no -- these kinds of pedigree studies -- and I would like to suggest, by the way, that this is not just a problem in the genetics area. This is a huge issue for the social science people. This is psych research, this is anthro research in a big way. So those two huge fields are affected by this.

That in those areas there is one person who is, in a sense, the subject of interest. And information that is revealed about third parties like an aunt or an uncle or somebody else who lives in the same town, those people are not subjects of interest even though information is being revealed about them. And in that way the word "subject" actually, which we have abandoned, would be kind of helpful in helping us to articulate what we are trying to say.

It seems to me that this then opens up the possibility of focusing not on a definition of a human participant because as soon as we get into definitions

we get into problems about whether what we are saying is intrinsically true or not but focusing not on who should be covered and who should not be. That is a little bit different.

And to say that the people who should be covered by all of these recommendations are the people who are the subjects of interest, but that we recognize in a variety of settings that research with the subject of interest reveals information about third parties and that this is a classic problem now of risk management because that does pose risks to "society" and particularly those individuals.

And then we begin to get a little bit more specific about the kinds of things that IRBs might want to think about doing. They should be thinking about ways to accumulate that information in a fashion that makes it as difficult as possible for it to actually be revealing.

Now I come from a relatively small city now. If somebody were doing research that I volunteered for at the University of Wisconsin and they are looking at smokers and the addiction patterns in their families to understand the origins of the penchant for smoking, they would start asking questions that could include questions about whether my mother or father had any

addictive behavior or if there was any OCD in the family.

And if I started answering yes and no and yes and no to alcoholism and OCD and, you know, youthful drug use, there is an excellent chance that the investigator might know my relatives because it is a small city. And if they are all living there, you could easily -- these are real issues about real stigmatization and harm where IRBs could give guidance about pay attention to who is going to be doing the interviewing. Pay attention to whether or not you are using last names. Pay attention to whether you are asking about family relationship or actual names of the people. And this should be part of the IRB discussion about the reduction of risk at the outset.

I think we can achieve a role for this research without it being hamstrung but also without -- I do not want to just sweep it under the tables. I think it is a very genuine problem.

DR. SHAPIRO: I want to go back to what we actually said in a moment but let Steve and Bette speak and then I will make my point.

MR. HOLTZMAN: I want to endorse what Alta said but I actually think it is all there in the report and we just have to bring it out because if you look at

the history of our reports, if you go to the tissue sample report, we say in general genetic studies are minimal risk but consider the nature and whether it is stigmatizing. In other reports we have talked about the involvement of community -- not community --

PROFESSOR CHARO: Right.

MR. HOLTZMAN: -- if it is all the same principle as being aware of the impact of the research beyond the subjects themselves or I guess what we call participants and how that should enter into the calculus but not trying to jam it into this narrow window of the definition of participant, which gets into all sorts of issues about the autonomy and what does it mean to respect. So if we -- I think it is there and if we just sort of call it right out that maybe there has been a tendency given that the only way you had to protect -- to think about protections was via calling it a subject, you get contorted so let's not contort. Let's just call it out. And I think we go in that direction.

DR. SHAPIRO: Could I just -- I know, Bette, you are next and others but I just want to see if my memory is correct here. My memory is that our recommendation in Chapter 2, which lists who it is that is a human participant, and that is what sort of brings

in the -- all the issues. It had a condition in there which was something like information about them is accumulated and analyzed. I do not have the -- I am not quoting.

PROFESSOR CHARO: 2.5(i) and (d).

DR. SHAPIRO: Okay. That is 2.5. Thank you. If I understand what is being said around the table now is that is not a good idea. That is you do not want them -- and I think that is the point that Bette is making -- although, Bette, I do not want to speak for you -- that really in 2.5 that should not be a category which creates someone as a human participant but rather, if I understand the nature of all the comments being made, that this should be recognized as a risk which IRBs and others ought to consider and then deliberate about and make whatever recommendations seem appropriate to them in the context.

That is how I have understood what has been said but I just want to make sure that I am not misreading people.

PROFESSOR CAPRON: But, you know, I agree. In 2.5(d) there is a (1) in there that we do not need but point (d) says it is identifiable data about them or collected or analyzed for purposes related to the study. There is then a statement, which is to me

totally opaque, which goes on and says the definition should not include...information revealed about others.

Now does that mean that if the only thing you got from me was information about my relatives, they would all be participants and I would not be because I had only revealed information about others or because what I am revealing is information about others, they are not participants? I mean, I do not know the answer to that question in reading that recommendation.

MS. KRAMER: And then you can go --

DR. SHAPIRO: Bette, and then Arturo.

MS. KRAMER: And then you can go back and read the text where we talk about others who are identified and you can talk about identifiable material and that is why what I am saying is I think we need to be very unambiguous about what we are saying because as Alta points out this is not just genetic research. It really -- it is reflected across many different kinds of research.

As I thought about it, both before and then during and then after, another point where we get into trouble, of course, is where we have said that all coded material is identifiable. And that also creates a lot of problems in terms of who then do they -- you know, do they then have to go back and consent or do

they have to consent all the people who are going to be identified.

Ironically, sometimes they can be asking a question not even having -- or -- and get information about others. I mean, Marjorie pointed out an excellent example to me where they were doing studies of -- a study was being done about the age -- the age at which young women first had sexual intercourse and they were asked at what age a women was at and she said, "At the age of 15." "How old are you now?" "I am 16." "Is that person still a partner?" "Yes, it is my father."

Well, you know, they did not consent the father ahead of time, you know. They certainly now have information about him.

But I was losing my train of thought. As I reflected where the problem was, it seemed to me that these were really issues that needed to be dealt with where these people really needed to be protected by addressing confidentiality. Confidentiality of the data and the need for the researchers themselves to maintain a very high degree of confidentiality as opposed to dealing with these other people, the others about whom the information is revealed as human subjects themselves.

DR. SHAPIRO: Okay. I have quite a few people who want to speak. First, Arturo, then Bernie, then Alta.

DR. BRITO: I had made a comment in one of the e-mails about the proposed recommendation 2.5 and the definition and it is interesting how this conversation has now come back to one of my concerns.

So the first question is do we identify individuals that are providing -- that are giving information -- let me see. When an indexed participant, when an indexed subject in a research protocol provides information about individuals other than himself or herself, do we consider them participants also? That is the first question but I do not think that is the primary question.

The primary question revolves around two issues. One, confidentiality and, two, which is related but not necessarily always comes together with it, is whether or not that participant -- if we call them a participant -- becomes identifiable. And I think those are the main issues and the reference I made in the JAMA article, for those that are interested, I have a copy with me, I think deals with this very well. And I think that is where we need to really focus our attention on and make -- possibly

within this recommendation, discuss that or make a separate recommendation that we feel that these two issues should really be primary focus.

But in terms of trying to get consent forms from people that are not part of the -- or the index participants in a research protocol, I think that is a bit ludicrous in some ways because I think it would stop a lot of useful research and a lot of it that really would not affect people in the negative way.

But I also want to go back to something Alta said later that one of the things that came across in reading this -- some of the public comments about the report is the de-emphasis on things other than a biomedical model and this is where social science research, anthropological research, et cetera, can be rather harmful because of stigmatization problems and I think that is where those -- that type of research really needs to be emphasized again and this is where it needs to be, too.

DR. SHAPIRO: Thank you.

Bernie is next.

I just want to make a comment because of one of the things that you have raised, Arturo. And that is the issue of whether we have adequately dealt in the report with issues that surround so-called social

science research as opposed to biomedical research. And I think while this may not affect our recommendations, I think the text actually does not do an adequate job of that in my view. And so we will have to go back and do something about that.

I am not sure. I think Bernie, also, may have made that point. I do not remember any longer but you gave me a lot of points, but anyway you are next.

DR. LO: Yes. It seems to me that this is an example where you really have to sort of piece together several recommendations to put them all in context in any particular case. And it strikes me that we should have a text -- a side bar illustrating maybe the case that Alta raised or some other social science/genetics case and say let us illustrate for you how the various recommendations play out in an interlocking way.

I mean, first we say, no, these are not subjects in the formal definition but that does not mean we ignore them. We take into account what risks and benefits might fall to them and the investigator and the IRB have to weigh that and make adequate precautions.

We still call it coded but that does not mean that you have to go out and get consent from them because if you look back at where we say we presume

that you do not need consent for this type of research provided that you protect confidentiality but there is a particular sort of variant here because of state reporting laws about child abuse that is sort of the exception to the exception.

And so if we play it out, people can then see how in an individual case these recommendations work out. In the abstract it is very hard to figure out but by giving a specific example like the ones that Bette and Alta are raising and illustrating it, I think it can show people that we do not have to sort of tinker with the definition. We just have to read each recommendation in the context of the other recommendations we make.

DR. SHAPIRO: Okay. Alta, then David.

PROFESSOR CHARO: Well, I actually do not disagree with much of what Bernie said, although at the very end when he said we do not tinker I would because I think there is actually a lot of tinkering needed for a lot of them but I think it would be very helpful to actually not require people to infer from a collection of recommendations what the position is.

And I agree with Bette that we should try and take this topic on its own, recognize that it is an emerging area of concern, and address it very

specifically even if it means that in some ways we are repeating things that are implicitly imbedded in the other recommendations.

My suggestion for what we would want to say is that we recognize that research involves in a sense the seamless web of knowledge but you cannot learn something about one person without having incidentally learned something about other people. It may be probablistic. It may be imperfect. It may be unproven but you are learning something about other people and it is a matter of degree.

Second, that we recognize the distinction between what Arturo is calling the index subject and what I was calling the subject of interest and all of the other people about whom things might be learned. And we distinguish them because the index subject is the person in whom we actually are interested in a variety of things. Whereas, the other people are of value only to the extent that the information reflects on the index subject. All right.

Third, that -- excuse me?

MS. KRAMER: In genetic research that is not necessarily true, is it?

PROFESSOR CHARO: Can you speak in the mic because I cannot even hear you?

MS. KRAMER: No. I say I think in genetic research that is not necessarily true.

PROFESSOR CHARO: Well, if the actual interest is in every member of the family then every member of the family is, indeed, a subject of research. I mean, I think we need to be able to make a distinction here between research in which you are actually studying five people simultaneously and research in which you are studying one person and in the process of studying that one person incidental information is being revealed about four others.

MR. HOLTZMAN: Bette, the way she phrased it was exactly right for genetics because if you are my index, what makes the information about your parents' family is what makes me interested in you. If I actually want to get a sample and information about them, just like she said, then they are also a subject. She nailed it.

PROFESSOR CHARO: And this is something that is actually going to be subtle in some cases. I think that it would be impossible, and that is another part of our recommendation, I think it would be impossible to make this categorical in the sense that we have to get -- we have to treat all people about whom incidental information is revealed to subjects or that

we never have to treat them as subjects. I think either position is likely to miss the boat on some number of protocols.

I think that what we want to say is that when an IRB is looking at a protocol in which part of it involves having the index subject reveal information about other people that the IRB should now be looking very closely at (a) whether at any point it has now been transformed into a protocol in which we are genuinely studying those third parties;

And (b) if that is not the case, if we are not genuinely studying them but nonetheless information is being revealed that part of the IRB's job is to work with the investigator to minimize any of the indignities as well as actual risks of real harm that might be associated with having personal information revealed by the index subject about these third parties.

And we do eventually throw it back to the IRB but we throw it back to them with some idea of what they are supposed to be doing and in that sense I think we clearly state that we do not think the categorical approach, which is what you fear OHRP is learning towards, we do not state that we endorse that but we do recognize that this is a genuinely subtle area where

occasionally we need to be a little bit more careful than we have been.

DR. SHAPIRO: Bill?

MR. OLDAKER: I am interested in a robust system that regulates here. I think one of the problems with it -- I hear what Bette has pointed out -- is that if those who are being regulated cannot determine what, in fact, is being regulated that is going to cause people to have disrespect for the system, so I would suggest that -- and I understand what you are saying, Alta -- I think the clearer one can be in defining what is, in fact, going to be covered here and pointing out that there always should be a fear of bureaucratic creep where the regulated does not know exactly what is being covered. I am not sure how we spell that out but what I have heard from Bette was that people were saying, "Well, we did not know that that was covered." And I think that is the biggest risk here, I think.

So however we draw it, we draw it in a way that makes it as clear as possible that there are bright lines around it that people will be able to see what is attempting to be regulated and can rely on that. Now I am not sure exactly how you do that but ofttimes we will worry about it from the other side.

We want to make the definition so that it stands by itself and will cover almost any contingency out there and I think that is how we have written it. I do not know if it can be written the other way but I am just suggesting that is what I am hearing from Bette and what the fear is.

DR. SHAPIRO: David?

DR. COX: Yes. So, Bill, I think you are right on target. I wanted to combine what you said with what Bernie said because I think maybe Bernie's answer was the solution, a specific example. This specific issue of probands and related individuals is one of the most contentious in genetic research and it has been going on for 50 years in a whole variety of different settings.

And it is not accepted internationally at all in terms of what is the best way to do it. Bartha Knoppers gave a talk a couple of years ago at the American Society of Human Genetics about what one's obligation was if you found out something from a proband to the rest of the family.

And Bartha representing a European point of view had a very different point of view from the other 2,000 people sitting in that room, and they almost booed her off the stage, which was the American point

of view. Which is it is only the proband, you have no real obligation or right to talk to anybody else unless that proband tells you to do so.

So the genetics community has this very -- in America at least -- has a very clear view that the proband is what it is and these other people, you know -- you know, there is like a magic glass wall that separates you from them and that protects them in a way.

So how do you deal with that? Well, it is not surprising to me that people are going berserk when you are starting to talk about, you know, including those people as part of human subjects. So Bernie's suggestion, I think, is a really helpful one and actually Steve and others have said this, too. Let's use a specific example of how we work through the regulations and how it applies because to be perfectly honest a number of people would like to use these very gray areas to say that the whole system has no merit and it is unusable. So I find these gray areas the most useful to lay out and show -- see how cool the reds are because even in these gray areas it works.

So, Bill, I think a specific example maybe --

PROFESSOR CHARO: But what is -- can I ask what your position is on whether or not they should, in

fact, be treated as subjects?

DR. COX: Yes. So --

PROFESSOR CAPRON: He takes the American view.

(Laughter.)

DR. COX: I actually take an Asian view.

(Laughter.)

DR. COX: It is whatever -- look, the -- it is the view that I had on the tissue samples and everything else. It is the view Steve articulated, which is that you have individuals who are human research -- the view you have, Alta, that you have individuals that are research subjects but then you have associated data, the people themselves are not research participants but they are in a special class, that you have to consider them differently than the average man or woman on the street, period. They are not regulated under these laws, under these rules, but that --

PROFESSOR CAPRON: What do you mean they are not regulated?

PROFESSOR CHARO: They are not covered --

DR. COX: They are not covered by these.

PROFESSOR CAPRON: Their interests are covered but you do not have to get consent.

DR. COX: Indeed. Okay. Indeed. So I am not

in favor of changing anything. I am just in favor of what Bernie specifically stated. Take the regs and use this as an example and show how they apply to it.

DR. SHAPIRO: Thank you.

Bette?

MS. KRAMER: I like those suggestions. It may call for more than one example just because there are so many different particular areas that are covered and I would hope that what we would do is we would draw this bright line about whose concerns are dealt with how. For instance, who is actually the subject that needs to be consented?

And then whose -- what other individual's concerns need to be dealt with through issues of confidentiality and then a particular area where it is troublesome is when they are doing research on mental conditions because -- so all of those issues. All of those issues or at least most of those issues are considered to be very stigmatizing so then it becomes all the more sensitive.

DR. SHAPIRO: Okay. Thank you.

I think I really do sense consensus on this issue and it is very helpful, Bette. I am very grateful to you for raising this issue. It will, of course, impact directly on Recommendation 2.5 and the

stuff around it. I do not want to redraft that sitting here today but we may redraft it some time during the day. So it is very helpful to have had that discussion and we will get a chance to come back to it but I think we have a general sense of where we are.

I think we all agree that the people, these so-called secondary persons, have interests which have to be taken care of but they are not subjects in the sense of needing to be consented and so on and are not human participants in the way we define them here. So that has a number of implications for Recommendation 2.5 and we will have to come back to that.

Sticking on the same issue, I am going to turn to Eric now on the same issue of -- that surrounds recommendations -- again I guess it certainly involves 2.4. I think my recollection is that -- 2.5, excuse me. It is the same recommendation. The last line of that recommendation talks about the definition should not include "deceased individuals" and then it has -- followed by two other categories. Namely embryos and fetal tissue there.

Those are obviously very sensitive issues which we really have not discussed in any detail here and obviously there are -- I do not have to tell anybody on this commission those are strong words and

the question -- but we do have to face and discuss as a commission how we want to deal with that and what is -- do we want to sort of focus on that, do we want to put that aside for some other time? We just cannot let it pass and we certainly cannot leave it stay there as it is.

So I did talk, I guess, by phone or perhaps by e-mail, I cannot remember any longer, with a number of commissioners about that and Eric and I have discussed it and come up with a specific idea about how we might proceed but that is for the commission to decide. We just want to -- let me turn to Eric and see what one possibility is and then we will see if that seems suitable to other members of the commission or we want to go in another way all together.

DR. MESLIN: Right. Well, in the same spirit of the discussion you have just had, the text in your book is on page 42.

DR. SHAPIRO: Which chapter?

DR. MESLIN: Of Chapter 2 where there is a one paragraph statement that says "For purposes of federal regulations protecting research participants..." Chapter 2, page 42 "...we do not consider embryos or fetal tissue to be research participants." And it goes on to say that we continue to support previous

recommendations and refers to the stem cell report.

That statement sort of on reflection may not have captured what you want to say so there are a couple of ways of proceeding and just to lay out the ways of proceeding and you can declare these to be -- both of these categories to be research involving human participants, which is -- would be very much at odds with what you have said before.

You could be completely silent on the topic of you could indicate that there is -- there are areas of special concern that are so crucial that the commission need not take a position on whether they are or are not but that you will not be taking a formal position.

Handing -- we are handing out to you a paragraph that we put together just a day or so ago, aided in some ways by some e-mail that Alta and Alex at least thought about or helped give us some thoughts about. We were even going to go so far as to have a conference call to think about some of this but ultimately did not do that.

Which has the following statement, "The report and the recommendations proposed apply only to research involving currently living individuals and, therefore, NBAC takes no position on whether embryos, fetal tissue or fetuses are research participants subject to the

regulations governing human research. This view is consistent with our previous position on the use of human embryonic stem cells and embryonic germ cells. In our view research involving fetuses and embryos raise particularly sensitive issues, applying this report's recommendations to such research situations might yield results that were not contemplated or intended by NBAC. We further note that additional protections against in the DHHS regulations pertaining to..." and then we give the actual title of Subpart B and then mention that revisions of Subpart B were intended to be published during the previous administration but are currently undergoing review.

Now that is just a suggestion for how to be specific about what you should say because certainly from, I will say my perspective, being silent on this is not a good strategy and clearly unless you want to carve out a special exception, which I do not think you do, your options are limited to something like this approach.

DR. SHAPIRO: Alta, and then Steve.

PROFESSOR CHARO: I think this comes close. There are things I would want to delete because I do not -- I think they kind of raise red flags without adding a lot and in some ways to just very slightly

change the tone here. And it relates to the way in which we also talk about this in Recommendation 2.5. I would like to once again suggest that we not try to define a human participant but instead simply define the -- simply state to whom these regulations apply and they apply to people who are exposed to manipulations, exposed to interactions, who provide data, whatever, and then we have a very clear statement that says cadavers, right. And then discusses what does or does not happen with cadavers.

And then for embryos and fetuses say these regulations do not apply to research on embryos and fetuses, and in the text, as you said here, deleting the thing about NBAC taking no position. If it is not taking a position, let's not say we are not taking -- I mean, it is just I think all we need to be saying is that research involving fetuses and embryos raises special issues that are not adequately handled by these recommendations. Therefore, these recs do not apply to them. A different set of rules should apply to them.

Some of those rules exist, some of them are in revision, and we are not tackling the question of what those rules should be in the future. It implicitly takes no position but by saying we take no position, I can guarantee you that that is interpreted as taking a

position.

The absence of endorsement of one position or another in this debate is interpreted as having taken a position of opposition to those who think that only one position can be sensible and those people exist on both sides. So there is absolutely no way to win if you are going to even mention the idea that there is an intrinsic status as a human subject or not on the part of embryos and fetuses. I think the only thing you can say is these recs do not apply, different rules have to be developed.

So I would delete from "And, therefore, NBAC takes no position." Delete it all the way to "1999b: Then in our view research involving fetuses and embryos raises particularly..." I would say special issues rather than sensitive, and then leave the rest for the text. And then 2.5 needs to be redrafted.

PROFESSOR CAPRON: I would second that with removal of all the first person plurals.

DR. SHAPIRO: Yes.

PROFESSOR CAPRON: We need not say in our view. It is a statement.

PROFESSOR CHARO: Yes.

PROFESSOR CAPRON: Research involves special issues. Those are dealt with under Subpart B.

PROFESSOR CHARO: And then additional instead of --

PROFESSOR CAPRON: Et cetera.

PROFESSOR CHARO: Yes.

PROFESSOR CAPRON: I mean just simplification. I second it and would suggest that we table this until we have some alternative language in front of us.

DR. MESLIN: And no mention to having taken a position about this issue in stem cell.

PROFESSOR CHARO: See, I do not think we need to because this is about a general set of recommendations for human subjects research in the United States. That report was premised on the existing regulations and it had to be based on -- within the context of those regs -- what did the commission -- I exempt myself because I was recused -- think could or could not be done, should or should not be done. This report is different. This is about what the new system should look like.

All we are saying is this report is about the general rules of a new system and it does not apply to certain special cases and one special case it does not apply to is embryos and another one is fetuses.

DR. SHAPIRO: Bill, and then Steve.

MR. OLDAKER: Alta, I understood you to say

that cadaver material would not be covered. Cadaver material would not be covered, right?

PROFESSOR CHARO: Well, actually we need to talk about cadavers. It is a little --

MR. OLDAKER: Right.

PROFESSOR CHARO: Yes.

PROFESSOR CAPRON: That is the previous page.

MR. OLDAKER: Right.

DR. SHAPIRO: Deceased individual.

DR. MESLIN: That is one page 41.

PROFESSOR CHARO: No, I mean we here at the table. Yes.

MR. OLDAKER: Intellectually it is difficult for me to discern the difference between cadavers and fetal material.

PROFESSOR CHARO: Well, that is another problem here. It keeps talking about fetal tissue but it should be talking about fetuses, right.

MR. OLDAKER: Right.

PROFESSOR CHARO: And it is -- so it should be embryos or fetuses, not fetal tissue.

PROFESSOR CAPRON: It does say that.

PROFESSOR CHARO: It says fetal tissue --

PROFESSOR CAPRON: Yes, but we cut that sentence.

PROFESSOR CHARO: Oh.

DR. SHAPIRO: Right.

PROFESSOR CAPRON: Research --

PROFESSOR CHARO: That was cut out completely.

PROFESSOR CAPRON: -- involving -- add human -- research involving human fetuses and embryos raise special issues.

PROFESSOR CHARO: Right. And in the 2.5 it should be embryos/fetuses, not embryos/fetal tissue. But that needs to be redrafted anyway.

DR. SHAPIRO: Okay. We may be back to this issue, Bill, because it is important.

MR. OLDAKER: I was pointing that out.

DR. SHAPIRO: It is an important issue.

Steve?

MR. HOLTZMAN: I am 99 percent of the way there with you, Alta, okay.

DR. SHAPIRO: It is the one percent that separates all of us.

(Laughter.)

PROFESSOR CAPRON: Less than that.

MR. HOLTZMAN: Less than that.

(Laughter.)

MR. HOLTZMAN: And ten percent separates us from corn, isn't that right?

(Laughter.)

MR. HOLTZMAN: So I think part -- playing out your notion, some of the politics and rhetorics, on page 40 where we are talking about definition of human participant --

PROFESSOR CHARO: Did you say page 40?

MR. HOLTZMAN: Yes. I mean that is a subheader.

PROFESSOR CHARO: Yes.

MR. HOLTZMAN: I think what you are saying is maybe what we ought to be -- I had a definition for purposes of these regs or whatever, just -- or even avoiding the word "definition." I take what you are saying -- I mean, it is a definition but you do not want it to have the sense of we are taking a position of what is and is not a person. I understand that.

DR. SHAPIRO: Correct.

MR. HOLTZMAN: Right.

DR. SHAPIRO: I agree with that.

MR. HOLTZMAN: Okay. And I also think that, you know, the deceased individuals -- I think we probably had in mind information about them more than actual work on a cadaver. Maybe we had both in mind but it seems to me that if we sort of break that one out, and I am not sure that I would use those special

concerns, I think distinct concerns, right, and that the sort of preamble to this is that we are dealing with human participants where things like informed consent, et cetera, are in play.

That is not to say that is now the only set of concerns we have as human beings in society. There are other concerns around things which are not human participants in the relevant sense. For example, bing, bing, bing, bing, all right, and that that -- now are we suggesting anything in the way of a framework to think about those?

I think we are suggesting not to impose this framework. We are affirmatively suggesting that.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: The research on cadavers is a genuinely interesting problem and I remember an exchange with Alex about this a number of meetings ago. It raises the same set of concerns as the one about the index subject and the third parties except for one crucial procedural detail that affects our discussions and it is the same procedural detail that came up in the HBM report.

Specifically it is this: When you are working with a proband and incidental information is revealed about third parties you are working with a proband.

You are, therefore, doing research with a proband and there is going to be some IRB review and, therefore, there is some moment at which people notice that you are getting third party information and can decide what to do with it.

In HBM, as with research on cadavers, the initial question was whether or not you were doing something that counts as research that has to go through review at all. If the answer is no then there is no external body that has a moment to say to the investigator have you thought about the effects on these third parties, they are not formal subjects but nonetheless you need to be thinking about their needs.

In HBM we got out of that problem by calling it research and a key part of that was calling coded material identifiable so that it became part of the research endeavor and then we attempted to clear up the problem by having a rapid review of most to catch only the ones that needed it.

The question is do we take the same approach with cadavers or not? I am not in favor of doing that with cadavers because of the vast amount of material that throws no information on currently living people as opposed to the HBM where we were only talking about

--

MR. HOLTZMAN: You just included archaeology as well when you did that.

PROFESSOR CHARO: That is exactly my point. In the Discover magazine they had this really cool thing about an Egyptian mummy where it turned out they found the world's first prosthesis, you know, and I would hate to think that before they could have actually started working with this mummy they would have to go through an IRB. It seems superfluous.

But I think that we need to address this and acknowledge that there is now going to be a situation where there has to simply be a more generalized call for all people engaged in research to recognize when their work incidently throws light on third parties even if their research is not destined for external review.

PROFESSOR CAPRON: Actually I think Achtanabin (phonetic) gave consent to that research and it has been found --

(Laughter.)

DR. SHAPIRO: Yes, that is right. He found a signed form.

PROFESSOR CAPRON: That is right.

(Laughter.)

DR. SHAPIRO: I think this discussion on the question of cadavers, I think, again brings us to the same frontier, so to speak, as our previous discussion did. That is there -- it is really in a situation where you want to encourage people to think about these things but you do not want to carry in all the entire paraphernalia just because -- well, I do not want to repeat this -- that go automatically to but you do want to put some obligations somewhere for people to think through and to reach some kind of sense -- there is a lot of frontiers like that as we go through this and we cannot expect to eliminate those difficult areas.

MR. HOLTZMAN: Harold, you know, as I think about, Alta, what you were just saying, in the previous report all we had was the IRB.

DR. SHAPIRO: Right.

MR. HOLTZMAN: But if you take this in sum, we are talking about certification of researchers. Now granted some of these researchers would not get certification, I hear that, but it is a general call to people who are engaged in research or things that look and smell like human subjects research albeit not being human subjects research to be cognizant of this.

PROFESSOR CHARO: You could call for people who work with cadaver material to be certified and it

means they do not have to go an IRB. I do not know if you want to do it but you could say it.

PROFESSOR CAPRON: Remember one other use of cadavers that has been used, and I think the department has now abandoned this but they may still be doing that, is the Department of Transportation using corpses in crash studies and that is cadaver material in the form of a cadaver.

DR. SHAPIRO: We cannot get around that.

(Laughter.)

PROFESSOR CAPRON: But it is an example of something where they were always very insistent this was not a human subject and yet I think to the members of the public and to an IRB you might say that is true but there are considerations about the way that is done and with whose knowledge and consent it was done that still need to be taken into account even though it is not a human subject.

DR. SPEERS: And you may recall from the testimony from the person from General Motors who said the Department of Transportation did not consider cadavers human subjects but, in fact, they did and reviewed all research involving cadavers. So we have exactly that situation.

DR. SHAPIRO: Bernie?

DR. LO: It strikes me that this is another one of those difficult cases in Steve's term that really can illustrate how these recommendations might work out. I mean, I think we should just say up front there is a tension here between having regulations that cover everything and making the regulations so complex that they are unwieldy and that we recognize there are problems here and that nothing is to stop people from doing more than the bare regulations.

People can send it to the IRB voluntarily. People can have educational programs even though they are technically not required. And that good practices should take into account sort of considerations other than is it research and do you have to get consent in terms of protecting sort of decency and interest of people even if they are not your research subjects.

We probably should allude to Native America concerns about studying, you know, cadavers and other artifacts as being -- even if you do not identify the individual that may be offensive, I just think we have to say that these are concerns and that people can take steps to try and make sure these are resolved without unnecessarily having to make a specific recommendation on it.

DR. SHAPIRO: David?

DR. COX: Bernie, you just triggered something, though, in me, which again comes to the point of being really clear what is -- what the regulations apply to and what they do not. Because one of the things that is going on now is that -- I have seen this happen numerous times. Even though everyone acknowledges that a particular case is not covered by the regs that an institution says, nevertheless, I want you to put this through the IRB just to be safe. Now that is crap because what it does it is saying -- so do it anyway because I am not sure that somebody is not going to give us trouble about it so we are going to put it through the IRB.

So I think that that is exactly what we want to not have happen, is make it really clear what it is that the regs are applying to but point out that you can be ethical about having to have the IRB tell you it is okay.

DR. SHAPIRO: Two people want to speak, Bernie and then Alex.

DR. LO: Yes, just to respond to that. I think it is very useful, David, and I would say let's be clear that we are not suggesting people do it for defensive purposes.

DR. COX: Indeed.

DR. LO: But to say, look, you guys in the IRB have thought a lot about harms, risks, minimizing harms, help us think this through not because we are afraid that we need some cover but that we just want to make sure that we have done a good job.

DR. COX: And I am happy with that but to also give another option, which is you can sort of sit in the shower and talk with your other colleagues to figure this out and it does not have to be the IRB's blessing.

DR. LO: And there can be professional guidelines, all kinds of things.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: Well, David, I think there is a developing tension here around what we are up to because in the end we still buy in to the institutionally disbursed basis of research oversight and we say we are not here as regulators, we are not here drafting the rules. We may give illustrations and I fully agree that we can say to people there are a lot of ways that you can vet something ethically without going to the IRB.

But if an institution in this disbursed system says we believe that out of perhaps an excess of caution, not regulatory fear but an excess of caution,

we think a more formal process of having this vetted is desirable. I take it that we should say nothing against that. I mean, the whole idea that it is -- you have an internal issue at Stanford if the higher ups are telling you take this to the IRB and you say, "The rules do not say it has to be," and they say, "Take it through the IRB." And you may feel that is unwise but that is Stanford's mistake. It is not OHRP's mistake and it is not our mistake from your point of view it seems to me.

I just want to be clear that we cannot have a report which we were aiming towards a few minutes ago of saying we are giving the principles, we are looking at the goals, this is a more ethical system if people can get there, one which is to give the public more assurance, and that part of that is that IRBs and institutions are going to have to use their judgment to apply this. We cannot say that and then say it would be wrong for an institution.

DR. COX: Not wrong, Alex. Just give them another option because I can assure you if these institutions realize that there was a viable option other than covering themselves by going through the IRB, they would not have you go through the IRB.

Now I think in many cases --

PROFESSOR CAPRON: But it is not -- I mean, it is an option that exists every morning when you wake up, which is that you can talk to other people about your work and say, "I am troubled about this. Am I doing a good thing or not?" You do not -- it is no more or less an option whether or not our report exists.

DR. COX: What is happening in my view, the fundamental reason why the system is broken is because people abrogate any personal responsibility of figuring out what the rules are so what happens is everything gets reviewed so you do not have to think about it. And I am not saying that if people say this is one case that we want to be more careful about and so we are going to review it, I am happy with that. That is not what is in the aggregate going on.

What is going on are people not thinking about it at all and so --

DR. SHAPIRO: I think the -- you are both right. That is we do want to encourage people at all levels to think about it. That is what is behind the education issue. That is what is behind certification and accreditation that we will get to discuss but I think Alex is also right that we should not be in a position of telling institutions --

DR. COX: Not to do something.

DR. SHAPIRO: -- not to do something which they believe to be in their best interest for whatever set of reasons.

DR. COX: Right.

DR. SHAPIRO: There may be legal reasons which we are not even thinking about --

DR. COX: I agree.

DR. SHAPIRO: -- which might be driving them in that direction. And so that is part of decentralization, you just have to buy into it. If you buy one part, you get the other part. And so -- an that is a tension which often gets projected on to the rules and regulations which really should be projected on to the institution's own sense of what it needs to do and the burden is carried by this instead of where it really belongs, namely in the general counsel's office or somewhere else.

PROFESSOR CAPRON: Or the president's office.

DR. SHAPIRO: The president's office even. Nobody thinks the president is responsible for anything.

(Laughter.)

DR. SHAPIRO: Steve? I am sorry.

MR. HOLTZMAN: This is a totally different

subject. Just pragmatically, effectively what we are doing is an issues identification list today and talking about --

DR. SHAPIRO: Right.

MR. HOLTZMAN: -- aside from the first issue we talked about, about a new report.

DR. SHAPIRO: Yes.

MR. HOLTZMAN: It would be very helpful, I think, at least for me, is as new text is generated in the next version that we actually say here was issue one, all right, this is where it is specifically addressed in the text in terms of deletions and additions so that one is not confronted with having to go back and read the whole thing to find them.

DR. SHAPIRO: You are not the only one for whom this would be helpful.

(Laughter.)

DR. SHAPIRO: There is at least two of us and maybe more.

Okay. I think that is very helpful. Let me raise one more issue and then -- which does deal with some of the recommendations here and we will come back to it in a more detailed way when we go through those. And that is -- well, it is in some sense the most general issue that -- one of the more general issues

that Bernie raised in his e-mail. Namely are we generating more regulation, more bureaucracy to put it in a pejorative form than is worth it or without any getting additional protections. I think I am exaggerating what you said, Bernie, but you raised that issue a number of times.

And I am particularly -- of course, we ought to be sensitive to it. Bernie makes a number of very helpful recommendations about where in the text we could indicate that -- however people may evaluate our recommendations, our intentions were of a certain kind, and those are very helpful and obviously we will incorporate them into that.

But I wanted to ask a question about the establishment of NOHRO. Okay. The National whatever -- I can never remember what all those initials stand for, the National Office of Human Research Oversight, NOHRO.

Let me just tell you how I think about it. One of the -- in relationship to that issue. That is are we just establishing another mini-bureaucracy which will pursue its own interests rather than the interests that we are concerned about, mainly helping us all do better in the area of human subject protections. And that can certainly happen. Any time you establish an

institution it may lose its way and so there is obviously a potential danger that even if it were acted on positively that it would not function in the way that we had hoped. And obviously we have to recognize that and that is just a matter of speculation as to whether it would or would not work that way.

But I wanted to share with you at least what had been on my mind as I have heard this discussion of NOHRO and see if anybody else either has this same idea in mind or it is way out in left field or what. If I had to answer the question on day one when this gets established and we now have a new system, if it should be established as we indicate here, would things be easier and better? I would say no. On day one things would not be easier and better. Quite aside from the transitions there is a lot of learning to go on and so on.

And so my support for it had been based on the fact that -- of a dynamic that would get established over time, that as it developed ideas and as it developed guidance, and as it gave -- it sort of give greater and greater power to local IRBs over time, as issues were understood and so on, that, in fact, it is that dynamic that creates the better system, at least a chance to create a better system over time as opposed

to what would happen on day one.

And so as I look through the material we had on that in light of the comments that were made in those regards, it seems to me that if that is a viable way to think about it, that is really not talked about virtually -- it is talked about but not in a way that really comes across. I mean, I think you can find all this in the report but again I come back to on day one is it going to be better.

No, it will not be better on day one. It will be worse on day one but, hopefully, that would be a short transition period.

But is that kind of thinking consistent with what you all have in mind or is it just my thoughts? Bill and Alex?

MR. OLDAKER: That kind of thinking is basically where I was. I think right now the system is very confusing. People have a hard time figuring out where they are covered, what is covered, and I think that by making it simpler instead of having a number of different agencies speaking, having only one voice, I think is one of the important things here.

So I would say that, you know, look, there are always going to be people that criticize anything that is done that dramatically changes from the past. I

mean, that -- in anything I have ever been involved in, any time you change something there are a number of critics who just do not want the change to occur for any number of reasons.

But I think that -- I disagree with you a little bit on this, Harold, that I think that by placing the responsibility at one point and giving certain individuals responsibility for it, it is better off on day one because at least you know as the person who has an interest in it where the point is that you have to go to make the determination and, theoretically, you can get an answer.

So I think that I would argue that that would make it better on day one. I realize there would be a number of things to work out but -- so, you know, I look at it a little differently but, yes, there is always going to be some confusion when those things happen.

DR. SHAPIRO: I take the point. I have a number of people who want to -- Bernie, Alex and Steve.

Bernie?

DR. LO: I thought Alex was next.

PROFESSOR CAPRON: That is okay.

DR. SHAPIRO: I do not always get the order exactly right.

(Laughter.)

DR. LO: I think that is helpful, Harold, and I would go back to the discussion we started with about trying to make a distinction between the problems and goals we aspire to and the sort of procedures institutions were suggesting to achieve those goals and resolve those problems. I think if we can state that we think there should be simplicity, consistency from one agency to agency, accountability in Bill's terms, that is fine.

I think people can agree with that and still have very grave disagreements over a centralized agency. My daughter is learning how to read and write and she somehow has thought that the neatest thing in the world is to be able to spell out a sentence that says, "I'm allergic to broccoli and vegetables."

There are people now who are allergic to bureaucracy. Without even thinking about what is the bureaucracy for, is it needed, what are its benefits and risks, they say, "Big government, sounds terrible, I am against it. The people who thought it up are lunatics."

So I think given that concern or that position I would want to be very careful that our perspectives on what the problems are and what the goals you should

aspire to do not get rejected out of hand just because people heard a few key words and then throw out everything worth saying. You know, I think you could make the other argument that OHRP has demonstrated some of the problems with the bureaucracy.

I mean, the way they handled the requirement for education of researchers, many people in universities think was a fiasco. You scared everybody trying to get themselves certified by October 1. It turns out, you know, they did not really mean everybody but they did not think it through.

Bette's example is another example of people saying, "You know, what are these guys doing? They all of a sudden now have power, control. They are under staffed and they do not understand the issues. They are not listening to us and just saying this is the way we are going to do it."

Another approach is to say let's try things out, NBAC has highlighted some issues, consensus will start to emerge, and once standards, guidelines, agreement emerges, then it is a lot easier to sort of build a bureaucracy because we have agreement on the standards. Some of the public comments, I think, very -- were very concerned about setting up a bureaucracy in the absence of agreement on the standards so at

least it is a viable position to say you may get that office eventually but let's wait until there is a little more agreement as to how to do it, how not to do it, rather than to sort of give them a lot of scope for doing what may be good but what very well may be bad as well.

So I just have been concerned about our setting off red flags and then people stopping to listen to what we have to say.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: As a general prefatory comment I am concerned in our looking at our report and the comments we get on it to realize that the voices we are going to hear the most loudly from are people with a vested interest in the way the system looks now and those who have particular complaints with OHRP or OPRR in the past.

And I think our obligations to the public include a lot of people looking -- being concerned about a lot of people who are not well organized and they are particularly people who would be exemplified by some of the people who have been hurt by research in the past.

If we want to respond to that I agree with Bernie's thrust that what we said at the beginning of

the morning means that what we want to say is what objectives the system should serve and in addition to the adjectives that he applied, I think clarity and some form of responsiveness or flexibility is desirable. I happen to believe, Harold, that the system we have now grew out of what was basically an extension of the contract office, the research grants office at NIH and that is why we had the assurance system and everything else about it.

We are already saying vis-a-vis that that an accreditation model makes more sense than the assurance because the assurance is kind of negotiated at one point and then you do not really know what is going on.

But also at the national level we were concerned both about the lack of true authority in OPRR, these are government-wide things, and its undue connectedness to that research grant process in the sense of being attached to people who wanted to have research done as opposed to saying, well, there are other interests here that have to be protected.

And it seems to me that one can well argue that from the viewpoint both of the public and of researchers that an office which is clearly authorized to respond as things develop, and it does not take ten

years to get a change in the Common Rule because it is this ridiculous process in which nobody really has the authority to push forward and it sort of depends upon getting the right moment where you have the assistant secretaries of 20 departments and agencies ready to get their bosses to sign on to something.

It is a system which I would agree with Bill from day one should be better. I mean despite the transition. But I also agree with Bernie, we do not have to say the office has to look just like this or it has to be called the National Office of Human Research Oversight, whatever.

It does have to have certain -- it does have to serve certain goals and I think those are goals which even a person who has some allergy to government bureaucracy would realize are goals that they would endorse and are less bureaucratic and less cumbersome and more responsive and more accountable than the present system.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: If one lays out this with things that you wish to accomplish with any system of regulation and then say who is going to do it and what is going to be best accomplished from central versus local, you really only have a bureaucracy if you will

if you have got duplication after there is agreement on what needs to be accomplished.

So as I am sitting and listening to this, all of the reasons for centralization that we go into, I think, push for a central office but I find myself as I am thinking from my side, which is less about OHRP but more about FDA, are we clear if we had the central office tomorrow about what is FDA's responsibility versus what is this new office's responsibility.

So here is the tick list of everything that needs to be accomplished. Did we end up with any duplication? For me, the sponsor, is it clear to me who I have to deal with? And that is kind of a litmus test I would subject it to about whether it is a problem or not on day one. Okay. And I had not really thought that through sufficiently because I have been trying to be inhabiting more the NIH side of the house in listening to it.

So for those of you who are much more sophisticated about that, could you go through that test on this stuff? Is it really clear? I mean, the certification and all that? That is clear. That all goes to IRBs, right, but what about the other things?

PROFESSOR CAPRON: Accreditations.

MR. HOLTZMAN: What?

PROFESSOR CAPRON: Accreditations you mean?

MR. HOLTZMAN: Yes, accreditation, certification. What is the continuing role?

PROFESSOR CAPRON: FDA and NIH have already indicated, I think, that they are going to coordinate on that.

MR. HOLTZMAN: Yes. I am just saying take our system that we are recommending. Is it clear what are the roles and responsibilities of the -- of an OHRP that continues to exist, an FDA that continues to exist relative to the roles and responsibilities of NOHRO.

DR. SHAPIRO: Marjorie?

DR. SPEERS: Could I give just a quick answer? I will give you just a quick answer of how I think that would work and to think of it in terms of -- if you think in terms of the FDA regulations, FDA has specific regulations that deal with drugs and biological products and medical devices. And then they have a separate set of regulations that deal with IRBs and human subjects protection.

MR. HOLTZMAN: Right.

DR. SPEERS: So a simple answer, a way to think about it, as I would see it, would be that FDA continues to regulate the products, the drugs and the medical devices.

MR. HOLTZMAN: Focuses on safety and efficacy and not on the human subjects protection.

DR. SPEERS: Exactly. The human subjects.

MR. HOLTZMAN: Now were you saying the same thing about OHRP?

DR. SPEERS: No. We are not exactly.

MR. HOLTZMAN: No.

DR. SPEERS: Right. Because the roles are different.

MR. HOLTZMAN: Right. So what is the continued -- in that model you said there is a distinct set of responsibilities for which the FDA should continue to function and all that human subjects stuff NOHRO has got it. All right. What is OHRP doing since it ain't got the efficacy --

PROFESSOR CAPRON: It is implementing within the department.

MR. HOLTZMAN: What does it mean to implement within the department?

PROFESSOR CAPRON: Well, at the very least the researchers within the department have to have understanding of and implement correctly. They are going to have IRBs throughout their system that are in-house IRBs, the same way VA will. I mean, all these --

MR. HOLTZMAN: So intramural research.

DR. SPEERS: That would be one. I think that would be one piece of it but each of those federal agencies has a huge extramural program and so again what those departments need to deal with is the oversight system as it relates to managing the expenditure of those funds, which they do now through their grant management programs or their contract programs.

I mean, that is the biggest role that I see the federal agencies would have on the extramural side, which is equivalent in a sense -- it is equivalent to the way NIH or CDC would interface with OHRP now. They will still have to continue to do that.

PROFESSOR CHARO: I am confused now by that answer so I can ask a follow-up to Steve's? We are advocating for decentralized authority as it currently exists at the level of local bodies and the investigators and the bodies are all accredited and educated up the wazoo. Everybody is doing their job.

DR. SHAPIRO: That is a good phrase to use.

(Laughter.)

PROFESSOR CAPRON: I wish you would not get technical on us.

(Laughter.)

DR. COX: That is when you know you have done

it.

DR. SHAPIRO: That is right.

PROFESSOR CHARO: As part of the process of managing their grants and their contracts, the grants and contracts office always audit for compliance with any condition upon the grant. So whether it is that you actually filed, you know, your report on time or it is that you actually got the local IRB sign off that you said you would get, that is just part of the routine audit process to make sure that all of the usual rules have been followed.

So what is the extramural role again of OHRP and all these other equivalent offices in the respective departments and agencies?

MR. HOLTZMAN: Given that you have given to NOHRO review, audit, et cetera, et cetera, of those --

PROFESSOR CHARO: Well, you have given to NOHRO guidance, education, facilitation --

PROFESSOR CAPRON: And making of the -- and promulgation of the --

PROFESSOR CHARO: And promulgation of new regs so what exactly are these internal offices supposed to be doing?

MR. HOLTZMAN: Who has enforcement for example?

DR. SPEERS: I think what we have done is we have said that NOHRO would be able to delegate and should delegate responsibilities, some of the responsibilities to the federal agencies. So NOHRO develops the regulations, puts forward regulations, and then the various departments have to carry out those regulations and for their extramural programs because extramural programs do vary across the federal agencies, they have to then interpret and implement those regulations as they would apply to their extramural program.

PROFESSOR CAPRON: So if I am NIH and I give a grant, I can look to NOHRO to say grantee, here are the regulations, NOHRO has said this institution has an accredited IRB, and all the certification of its investigators and so forth is in order. Now this particular investigator I have given the money to does not get consent from people. He forges forms.

That is now my agency's own implementation of our grant and if we are going to investigate that, we have got a report from somebody at the school that these forms are being forged, and we go in and look at that, we pull the grant and we discipline that person. That is not NOHRO, right? Is that what you are saying?

DR. SPEERS: Yes. I mean, what we said with respect to enforcement was that NOHRO would become involved with serious violations or repeated offenders but that the agencies could deal with -- would be the front line or the first line to deal with issues of noncompliance.

PROFESSOR CHARO: I am sorry. But I could have exactly the same protocol having to do with survey research, both qualitative and quantitative, on personal behaviors associated with health promotion and degradation, right. You could do it. You know, you are looking at people with regard to their -- let's use the addiction model again like smoking and so you could have exactly the same protocol where your grant comes from NCI because it is a cancer-related thing or you are getting it from NIAID -- you are getting -- which agency does the addiction research, NIAID?

DR. SPEERS: NIDA?

PROFESSOR CHARO: NIDA, sorry. It is NIDA. So you could be getting the money from NIDA. You could be getting the money from NSF perhaps. What I had assumed was one of our goals was that it does not matter where you got the money. How you do it, what is acceptable, what is not acceptable will not change based on here you got the money. And that when you are

an investigator putting together the protocol and you are a review board looking at the work and signing off on it that you do not have to pay attention to the name of the sponsor, the rules are not changing on you.

Will we be accomplishing that with what you are outlining?

DR. COX: But, Alta, interestingly, this is exactly the issue of your individual institutions or your individual sponsors may for their own purposes, you know, have you do certain things in a framework --

PROFESSOR CAPRON: Yes, at the institutional level. Yes, and that -- we cannot do anything about that.

DR. COX: And, also, at the granting level agency, too. So that does not mean that the rules have changed. It is how people are applying those rules.

PROFESSOR CHARO: No, see, that is exactly what I am worried about. I do not want them applying them differently. I do not want to have to -- if I am sitting on a board where my goal is to help investigators figure out what is acceptable and what is unacceptable, I do not want to have start becoming an expert in the internal politics of NIDA versus NSF.

PROFESSOR CAPRON: That was the whole reason for the Common Rule because when the President's

Commission looked at this it was worse than what Alta described. The underlying regulations differed so if you were submitting to each of those three agencies, what you had to say in your grant application could differ because they had small and insignificant but nevertheless RSAL differences you had to take into account. And the idea of the Common Rule was there would only be one rule.

PROFESSOR CHARO: I understand.

PROFESSOR CAPRON: And what you are saying is doesn't that -- shouldn't that be an actual application rather than just on the regulatory --

PROFESSOR CHARO: If the interpretations are going to vary dramatically enough that I have still got to worry about this then I do not think we have accomplished the central purpose here, which is to facilitate research while maintaining an ethical grounding for it. Instead what we have done is we have created obstacles to research without necessarily increasing the degree to which humans are actually protected.

DR. SPEERS: Let me give a --

DR. SHAPIRO: Marjorie and then Trish?

DR. SPEERS: Let me give a --

DR. SHAPIRO: And nobody interrupt.

DR. SPEERS: Okay. Let me just give an example because I am talking about something that is very nut and bolt from a federal agency perspective. The -- for example, one of the requirements might be for extramural research, which it is now, which is no research funding may be spent until the IRB has approved the project and all the other necessary protections are in place. Okay.

Now if your funding mechanism is a grant that -- an R01 grant then you proceed in one way. You being the investigator or the institution and the federal agency. You proceed in one particular way and you are all familiar, I am assuming, with the NIH model of the peer review process and having everything in up front before the research begins.

But let's say that instead of a grant what is given is a cooperative agreement and that the first phase of that cooperative agreement is going to be one year of planning. So the first year of funding is one year of planning. And then the research is going to begin in the second year. The second year of funding.

So the same rule applies, the general rule of no research dollars may be spent until everything is in place, but the critical difference for those in the

field is when do you get IRB approval. Do you do it in the grant mode of have it up front or do you get it in the second year when you know what you are going to do?

And that -- that is a very nut and bolt example but that is the kind of issue that is very bothersome and burdensome in the system now because that kind of flexibility does not exist. I mean, I would agree with you that the ethical principles should be common across all the agencies and should be followed consistently but there are these kinds of issues, very practical issues that I think has to vary in order to make the system work because the agencies conduct their business differently.

DR. DUMAS: It seems to me that if the principles, the rules, the regulations were general enough it would allow for that and I think one of the things that has been of concern is that we do not make them so specific that they are -- that flexibility is not there.

See, I see this over arching structure as -- I see the various agencies as working in a subsidiary relationship to this over arching structure. They have the responsibility to conform with the general principles and rules but they should have some

flexibility to adapt them to their particular programs and I think the statement of the regulations should be such -- and many of them are -- so that it does leave that openness for people to adapt to their programs without violating the basic principle.

DR. SHAPIRO: I probably should not be speaking on this because I do not understand all the details of who orders who to do what in the various federal agencies but I think we are up against -- there is a limit to how far we can go insisting on commonality because of just the way the --

PROFESSOR BACKLAR: That is right.

DR. SHAPIRO: -- both the politics and the administration of the federal government are organized, and these compartmental lines reporting to different congressional committees and so on, does leave a degree of flexibility in departments which they are free to impose if they wish to. So I think we -- there are some limits on any recommendation we or anyone else can make that would really force everyone to do exactly the same thing in like circumstances.

And what we have to hope for here, it seems to me, is that NOHRO or whoever else it is lays down principles which they would all find acceptable but its implementations may, in fact, be somewhat different and

may not eliminate all the frustrations you talked about. I think it is -- you know, I do not know how we can get to that, frankly.

And the big issue about regardless of funding that we are dealing with here, of course, is an additional one to the one that you recommend, that is whether privately funded research ought to come in here. That is the big change we are making there if anything should happen here.

The other is a significant ongoing problem and I agree with you but I think there is a limit to how far, if I understand the way the government works, that we can eliminate this.

Now this planning example which I had thought about, the one that Marjorie just talked about, you know, could be handled in various ways. That is in the planning phase you do not -- you are not involved in the human subjects research yet. And so there is no reason to get an IRB review and there is no reason why the -- in my view why the federal government should hold up funding for the planning research pending IRB review because it is not yet human subjects or human participants, whatever word we are going to use here.

But, look, let's -- we have covered quite a few issues here.

PROFESSOR CAPRON: Trish?

DR. SHAPIRO: Trish, yes, you are the one that has been waiting.

PROFESSOR BACKLAR: No, it is all right.

DR. SHAPIRO: We have exhausted you by our impertinence. Thank you.

I think it is a good time for a break. Let's reassemble at 11:00 o'clock.

(Whereupon, at 10:43 a.m., a break was taken.)

DR. SHAPIRO: We have two important items on our schedule here. One is lunch.

PROFESSOR CAPRON: There is public comment.

DR. SHAPIRO: And one is public comments. Public comments is scheduled for 1:30, which means in -- with -- just out of respect for those who might want to give us public comments, I really want us all to be back here at 1:30 and lunch -- Eric will make some announcements. There are some places within a block or two where we can choose to have lunch and I will ask Eric to make that announcement just before lunch but that means we will adjourn promptly at 12:00 so that we allow enough time and all of us can be back here at 1:30.

Well, I thought that we would now proceed more specifically with the report itself that is in front of

us.

Excuse me, Trish.

PROFESSOR BACKLAR: I did not want you to forget me.

DR. SHAPIRO: I will not forget you. Is there an issue you would like to raise? A specific issue?

PROFESSOR BACKLAR: Yes.

DR. SHAPIRO: Right, I did not know whether you still wanted to speak at all but, fine, we will turn -- our first order of business will be to turn to Trish and see what issue is on her mind that she would like to share with us.

PROFESSOR BACKLAR: It is not a new -- can you hear me? I cannot tell if this is on.

DR. SHAPIRO: If you talk closer. I think you need to speak --

PROFESSOR BACKLAR: Yes, you can hear me?

PROFESSOR CAPRON: Right.

PROFESSOR BACKLAR: Okay. I just wanted to -- it is not a new issue.

DR. SHAPIRO: That is all right.

PROFESSOR BACKLAR: But I realize as I hear the -- part of the discussion that was going on that we were forgetting something that Bernie said that I thought was very important and that the

recommendations, that by doing our little preamble or vision, we are going to set forth the goals, and that will enable us in the main report not to make this more suggestions of how people do this, and not get quite so bogged down in all of the details of how it should be done. That is all.

DR. SHAPIRO: Well, fine. We are going to go through the report now.

PROFESSOR BACKLAR: Thank you.

DR. SHAPIRO: Chapter by chapter. Hopefully, keeping our -- well, when we get to the actual recommendations that are in these chapters there may be very specific ideas. For example, Alta mentioned before something with respect to 2.5 and other issues may come up.

So as we go through these chapters I am going to turn almost immediately to Chapter 1 and ask for any observations people have. It really would be helpful if as you think about the observations you might have that you distinguish between those that I might call issues of tone and characteristics which you would like us to address, which we certainly can address but we ought not to address those in detail here. We cannot do that kind of writing here but those observations may be extremely important and so I certainly want to keep

track of them. So as we write this we can address those.

And then there are specific issues, the nature of the recommendation is right or wrong or what you said here is right or wrong, I want an answer to that. And so as you make your comments if you could identify what it is that you are interested along those kinds of characteristics, it would help us know whether we can just accept the observation and agree that it shall be reflected as best we can in the next draft of the report or whether it really is a specific issue which you think we really have to focus on in a quite different way. That would be helpful.

And while there are many, many ways to go through this document -- indeed, we discussed a number of matters that are only focused on Chapter 2 or essentially focused on Chapter 2 this morning already, we could begin with Chapter 2 but just in terms of trying to get some things going and doing it systematically, I am going to ask for any observations people might have on Chapter 1, which of course is a kind of background chapter and then go to Chapter 2.

If there are purely editorial suggestions, that is the sentence structure really makes more sense this way than that way, those are extremely important

because -- but those, I think, we can give directly to Marjorie and have them incorporated in. So any observations you have in that regard that you either are willing to share with Marjorie by e-mail or just hand in your corrected pages, pages you think ought to be corrected, we can handle those things in that way. That has been very effective in the past and commissioners have been extremely helpful in that regard.

So let's go ahead with the three-quarters of an hour that we have left and at least begin by focusing on Chapter 1 and let me just ask which commissioners have some observations they would like to make about this chapter.

Alta?

DISCUSSION OF DRAFT REPORT: CHAPTER 1

PROFESSOR CHARO: With regard to the degree of emphasis on social science research and humanities research, page 36, and there is one other quick comment a little bit earlier on, are the places where you find it mentioned. I would actually like to suggest that we pull out with a heading so it is identifiable, easily found, something that says, you know, special concerns and whatever about social science, humanities research, and clearly says there has been a problem. Research

regs were designed with a biomedical model.

The model does not always apply very comfortably and social scientists and humanities people are increasingly doing research that raises privacy concerns that actually have real risks. They should be handled but that we also acknowledge that as a class this research tends to raise these problems less frequently and with a lower degree of severity and that a system needs to be developed that incorporates this research and at the same time, as we did with HBM, clears out much of this research rather rapidly for -- in order to not create some kind of obstacle. And to make it possible for people in those fields to find themselves reflected vividly and easily.

DR. SHAPIRO: Thank you. I think that is very helpful. I have also written -- not done that but I have written some text which actually -- I hope will go on pages one or two, which just does not deal as effectively as you said but sort of reflects it early on. I am not going to bother repeating that right now. It really dealt more with humanities and the social sciences. But that is just by way of small introduction but I think doing something later on in the chapter as you suggest could be very useful and I appreciate that comment.

Other comments, questions? Alex?

PROFESSOR CAPRON: Well, some of what concerns me a little bit about the chapter will probably be dealt with when we do the new version but it seemed to me that it got down a little bit too much into disputes and discomforts between IRBs and OHRP/OPRR. For example, the discussion of the annoyance people feel that the guidance that OHRP gives focuses too much on the regulatory issues and not enough on the principles, I see that as -- in a certain way in contention with our own desire to have people have clear guidance.

I mean, it would be fine to say just as we now see the need for our report to have the vision, the principle basis, this is the approach that will work, it would be fine to say OHRP could do more of that and the educational interactions should emphasize that more.

But, frankly, talking to some IRB people, they are happy to have someone give them an illustration of a problem that they need to avoid so that they do not have a compliance problem and not having a quorum or having a process in which basically one person on the committee reviews something, gives the view, everybody else on the committee has not really attended to it at all, and you end up not with a committee process but

with a whole series of individual reviewers as it were sitting around the table, each with their one protocol, and saying that does not achieve what it is supposed to achieve.

I do not think we should beat up on OHRP for that. I mean, I think it is helpful. It just should not be the only thing they do. So maybe it is a matter of saying more what we would like to see rather than critiquing some particular document that they distribute about common problems and findings or whatever it is called.

I mean, I think we are getting down into kind of an internecine battle at a very picayune level when we get to that and I do not even fully agree that they ought to be beaten up for it but in any case it is better to say what would work better.

DR. SHAPIRO: Thank you. That was helpful. A number of commissioners have made the comment that we are insufficiently appreciative of the many positive things OHRP does and there is no reason -- it was not our intention, I think, in writing the report that we wanted to sort of focus on them as the bad people in this whole thing.

PROFESSOR CAPRON: Not at all.

DR. SHAPIRO: Not at all. And so that comes

up in a number of spots the way things are written currently in Chapter 1. And Bernie, amongst others, had made that point and I think we do have to attend to it. So that is also very helpful.

Could I ask a question about Chapter 1, which also came up or at least came to my mind as a result of one or two commissioners raising the Gelsinger case and whether or not we ought to use that case by way of illustration. Obviously it is not our job to investigate the case. We have said those kinds of things many times but whether it, in fact, is useful to refer to it just because of the many different kinds of issues it raises. It raises the issues of informed consent as a process rather than the moment. It raises issues of trust. It raises issues of conflict of interest. I mean, it raises so many issues even on the surface of it regardless of how this gets resolved. The question is, is it useful to use that as an example or is that in some sense inappropriate for us in the context of something like Chapter 1?

I just would be interested in people's views on that.

Trish?

PROFESSOR BACKLAR: What I would like to say is I am --

DR. SHAPIRO: Do you want to talk in the microphone?

PROFESSOR BACKLAR: I am not answering your question but if we decide to do this, which I think may be a very good idea because it is easier to understand many of the problems when you have an example, I would want us also to have a research protocol where there were difficulties which were not clinical -- to do with clinical treatment and that we should search around.

Because, first of all, I thought, oh, we should have Gelsinger and maybe this recent Parkinson's case but then I thought, no, that is not useful. What we really need is a case that will illuminate our concerns about social science research.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I would love the Gelsinger case but for the fact that it is a gene therapy protocol.

PROFESSOR CAPRON: And that is --

MR. HOLTZMAN: And because I think that that -- all of the issues you are pointing to about conflicts of interest, about consent and whatnot end up being obscured as soon as you start talking about gene therapy.

DR. SHAPIRO: You mean that people -- that it is sort of -- the spectrum of it just clouds their

thinking about what you are saying.

PROFESSOR CAPRON: But if we are writing it, we can write it to show that the gene therapy aspect is not distinctive on the issues that concern us. I think it ought to be possible.

DR. SHAPIRO: I guess what Steve is saying is that is -- people will not read it that way at least is his suggestion.

PROFESSOR CAPRON: Well, I mean, is the Tuskegee case -- I mean, there are ways in which it seems to me if we issue a report in this day and age it would be odd for us not to mention some illustrations that will be on the public's mind as it would have been odd in our international report not to mention the perinatal transmission of HIV research in Africa and Thailand and so forth.

I mean, that is what informed people and the reporters who write about whatever we say know about it and it is sort of that is in a way the provocation for some of the things we are saying. As the radiation experiments were and as the -- for an earlier generation -- the fetal research/Tuskegee and other things that led to the passage of the National Research Act in '74 and created the National Commission.

It would be odd not to have those somewhere in

the discussion.

DR. SHAPIRO: Larry and David want to say something. I do not have any particular attachment to that case. It is fascinating to me only by the number of issues it raises and it raises all the key issues.

PROFESSOR CAPRON: And they are not because they are gene therapy.

DR. SHAPIRO: It has nothing to do with gene therapy actually. But if there are other examples anyone can generate, I, you know -- that would be great, too. I am not tied to that particular case.

David and then Larry.

DR. COX: Yes. The -- I like the idea of examples and although that one case -- I quite agree with you, Harold, that deals with many different issues. I find it more compelling to demonstrate the wide variety of cases that deal with each of the different issues because otherwise one -- it seems like, yes, here is somebody that really screwed up one time but basically it only happened once and it is not really a big problem. And I can think of any number of cases where each of the different things that is in the Gelsinger that I think makes a much more compelling argument of why we need this report because it is a pervasive problem, not just one completely screwed up

case.

DR. SHAPIRO: Okay. Larry?

DR. MIIKE: I do not really think we should refer to it because the impetus for our report is much more than a reaction to some bad examples. I mean, it is the whole issue of uniformity and improving the system, and that came on way before any of these particular cases came up. If we have those kinds of discussions in the first chapter it would seem like we were reacting to some particular situation and we are not.

DR. SHAPIRO: Other views?

Well, I would find it very helpful. I am not sure where we should come out here but I would find it very helpful if any of you have cases or can point me to cases in the literature which deal with cases -- what I liked about the case despite its disadvantages but I understand equally well is the -- how so many issues arose in a single case.

So I do not want to focus on that because that is not our job but if you give me other examples we could perhaps construct something which would be telling and would not get us down the path of a single case, which is a problem.

Okay. Other questions, observations with

respect to the material in Chapter 1?

DR. MIIKE: Just one comment.

DR. SHAPIRO: Yes.

DR. MIIKE: I know we had this chapter rewritten to put the first positive emphasis on research and then get on to the issue about human protection but when I read it, it takes an awful long time to get down to the point of where we are in this report. It is sort of applying to research and then we get down to it, and after all the focus of -- perhaps we can have an introductory paragraph that says what we are addressing in this report rather than starting off about how great research is and then putting on much later in the introductory chapter about what the report is about.

I think that is a simple fix.

DR. SHAPIRO: No, I understand that. Helpful.

Any other comments with respect to this particular subject? Okay.

Thank you very much. Let's -- of course, you know, this does not close the discussion so if any of you have any comments, suggestions that might be useful, we are getting to have a pretty heavy e-mail traffic and we ought to encourage that.

Let's go on to Chapter 2 now, which there are

a number of issues I know we want to address. Some of which we have already discussed and others we have not.

Alta?

DISCUSSION OF DRAFT REPORT: CHAPTER 2

PROFESSOR CHARO: Several. There are several. I do not know if you want to focus on text or focus on recommendations or both.

DR. SHAPIRO: Both.

PROFESSOR CHARO: Okay. All right. Let me start with the recommendations and then I will go back on the text.

Knowing that these may be altered somewhat in light of what happens with the new volume 1, I am going to call it for the moment, I would -- first I would suggest that we recast these as suggestions rather than recommendations. There are examples of one way one might try to implement the goals that we are going to outline.

The second is that whenever we are reporting, we are reporting to the Office of the President rather than to the Congress and so as we had already discussed in Salt Lake City, and I thought we had already agreed upon, our language should not be addressed to what the Congress ought to do but should be addressed to what needs to be done, and it will be clear that some things

need legislative action and, therefore, only the Congress can actually carry the ball. But I find myself uncomfortable with giving directives to Congress since we do not report to them and would urge us to think of ourselves, continue to think of ourselves as an executive branch commission.

I find myself hoping that we can have a little further discussion about what we are getting at in the Recommendation 2.4 about the nature of research. Again as with human participant, I understand this to be not an intrinsic definition of research. I understand it as a way to describe the activities that we want to have covered by our recommendations, which is a slightly different beast. And, therefore, I am not looking for something that is a perfect Oxford English dictionary definition of research but something that conveys what it is that is covered.

And so I find myself puzzled by the meaning of number two having to do with anticipated results that have validity. I am not sure what it adds and my understanding of which activities are covered or not, that would be helpful to understand better.

And, second, although it may not appear in the actual language of the recommendation, in the text one finds absent any mention of the relational concerns

that help to -- help us to understand why certain activities might be appropriate for some degree of oversight.

I understand that we have gone around this and we have chopped it out of the recommendation but one of the key distinctions between the biomedical situation, especially in clinical trials, and the social science research is that the relational -- the relationships between the professional and the subjects are quite different.

And that the misunderstanding, specifically things like therapeutic misconception, that can arise in the biomedical model arise to a large degree specifically because of the relationship between a health professional and a layperson where a layperson can walk into the situation with the kind of intuitive expectation of loyalty and care that is directed solely at the subject when, in fact, the relationship is not that. It is one in which the loyalties are now both to the world of science and to the subject.

This kind of problem arises very rarely in social science and humanities research. Maybe to some extent in the anthro research where people come into isolated communities may be misperceived as somehow bringing a benefit but it is rare as compared to the

biomedical model. I think it helps to eliminate why some relationships demand extra attention and others do not. Why it is that in the end we may find it easier to clear out some of the social science and humanities research with what I would prefer to call an expedited review as opposed to an administrative review because I think it conveys the meaning of the process a little bit better.

And so in the definition of research and in the text attached to it I would love to see something that better explains why these are the factors that matter, especially with this validity thing and, second, to replace the -- to reinstate some of the relational concerns.

DR. SHAPIRO: Can I make a comment about 2.4, which is -- you appropriately characterized -- not a definition of research but trying to get a hold of the kind of activities you want to fall into this category for these purposes. I am not going to -- I will pass around later a new definition I worked on but this is what puzzles me about this one. I think "anticipate" is just the wrong word. What you anticipate is sort of irrelevant to whether it is in this category or not.

And so I think this definition does need to be reworked. I think it is -- and so I agree that this

2.4 needs some effort and later on I might have some suggestions that would work on that. I have not thought carefully about this relation issue, which you point out, which is a very important issue and whether that should enter it here or in some other way I am just not sure but that is an important issue.

Alex?

PROFESSOR CAPRON: Alta, I heard you raising several very different issues and I was not sure if you were attaching them all to 2.4. On 2.4 itself I was not clear, and I guess Marjorie is the person to answer this for us, what the three characteristics are supposed to do. And, in particular, whether one and three are enough to define what is research.

I am not sure -- I mean, I find myself struggling looking at two to say clearly the -- not clearly. I surmise. It is not clear. I surmise the intent is to remove from the definition and, therefore, from any sense that it is subject to oversight certain kinds of things and between the recommendation that went out and the one that is now proposed in light of comments and rethinking, it was clear that number -- the original one did a very poor job of social science research and I assume that that is why you had the broader language "or the anticipated results would have

validity “and that” what is learned answers a question."

But how is it that not implicit in one and three? You have the intent to generate knowledge and you go about gathering data to that end. What is the struggle here? What are we trying to avoid saying is or is not research?

DR. SHAPIRO: Marjorie?

PROFESSOR CAPRON: With this language?

DR. SPEERS: Okay. The intent of this was to try to define three characteristics of activities that make them research. The first one is dealing with the intent, the purpose of the activity. The second is saying something about the type of information that is collected. And then the third is saying something about how that information is collected.

Now we have heard -- I want to just go on because I am not saying that I am wedded necessarily to these in the sense that -- number one, one could say that number one, the intent of the activity really embraces both two and three. I mean, you just said if we have one and three do we really need two. And then others have said, "Well, if you really have one and two, do you need three?"

It seems that the essence of defining research

is really in number one, which is that the type of -- the type of information that is being collected is the type that helps us develop general principles or theories. That in a sense gets at this notion of generalizability to use the old term that is not -- that many do not like -- or to capture what is in two for the most part that what is learned can be applied to other kind of situations.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I am not sure that that is true so I want to take up Alex's banner for a moment. If we just combine three and one, and ask the question this way. Can you give me an example of a systematic collection and/or analysis of data the intent of which is to generate knowledge, et cetera, et cetera, which would not constitute research?

DR. SPEERS: From my own personal experience a lot of what is done in public health as a surveillance system is a systematic collection of data that yields information.

MR. HOLTZMAN: Generalizable knowledge, et cetera, et cetera. And that you do not --

DR. SPEERS: I am sorry. I would say in surveillance, not necessarily generalizable to the entire population. It may be generalizable to a

community or to a county or to a state. I mean, that is where the issue comes in on talking about something being a systematic collection of information that --

PROFESSOR CAPRON: So it is not research then. It is the practice.

DR. SPEERS: Yes.

PROFESSOR CAPRON: It is the ongoing public health practice.

MR. HOLTZMAN: That is an example where two adds something.

DR. SPEERS: Yes.

MR. HOLTZMAN: Okay.

DR. SPEERS: Or in health services research is another example.

PROFESSOR CAPRON: No, but it does not add anything. Pardon me. Because you would want your public -- ongoing public health data to also have validity. I mean, validity is not the issue here. It is whether it is a research activity or it is a surveillance activity that does not get called research because it is authorized under a statute or regulation that says the Public Health Service can go around checking how many people have X, Y, Z disease or what bugs are in the water or, you know, et cetera. And we say, well, that is not research, that is public health

surveillance.

But I mean how does it differ from research? Not because the activity differs but because it is done in a different context but it is still producing -- if it is not valid data about the prevalence of a disease and, therefore, the need for a public health intervention then the Public Health Service is not doing its job.

DR. SHAPIRO: Alta, David?

PROFESSOR CHARO: I think -- first, I think if it can generate this much discussion about what these words mean, it is clear that the words are not adequate yet.

Second, I again would like to return to the idea that we do not try to define research, which is what this is trying to do. And instead simply try to present the areas of activity that need to be covered and those that do not. That allows you to use an extremely general, very simple, very short statement about what is generally research, which might mean something like systematic collection of information where the intent is to generate new knowledge and theories. Right?

And then notwithstanding that, notwithstanding that research is generally covered, the following

things are not covered by these rules. And one might be ordinary practice of public health surveillance. Another might be journalism. Another I would urge strongly would be oral histories. Right? We should probably think -- or, you know, direct that somebody else eventually think about various kinds of student projects. Consumer survey research on, you know, food preferences. Educational assessment tools like they have already in the current regs. And then we know the list is not comprehensive and we know that we are also saying elsewhere there is a group that needs to be saying that they continue the list.

Then we also have a list of things that are included even though they are confusing and I think here is where you want to make it very clear that when there is practice combined with research as is frequently the case in a clinical setting that it is going to be treated as covered by these rules even though it has a purely therapeutic intent, right, where for example a physician urges her patient to enroll in the local clinical trials because it is a last ditch possibility for a person with an otherwise recalcitrant problem. But that we want that considered as research because that is a continuing area of dispute.

And we probably need to focus more closely on

whether there is an analog in the public health area in which there is a mix of practice and research that should be called research or should be covered as research under these rules but I find myself skeptical that any collection of words is going to accurately capture this picture so that what we want included is included and what we excluded is excluded, and that everybody can tell that without having to go through a Talmudic discussion to figure it out.

DR. SHAPIRO: David?

DR. COX: So I find it interesting -- and you are going to get sick of me doing this over and over again -- I find it interesting that one of the ways that the Belmont Report starts is defining or attempting to define distinguished research from practice. So Alta has already brought this point up, so that -- and Alex has made it, too. You know, why are you trying to make a distinction with research. You are trying to distinguish some things that are and some things that are not. So, number one, this has to be -- how you tell if something is research versus practice, meaning human subjects.

Now it is interesting what the Belmont Report does in this because for me I think it is right one. Is that it makes a very simple distinction of what

research is and it is something that --not collecting data, not the validity, but it is testing a hypothesis or asking a question. That is what the distinction is.

Now then I believe it is what Alta says, too. Then you make a whole bunch of things, specific things that are not covered and things that are covered. But that the -- to get to the heart of what the distinction is. You can collect lots of data, all right. To me that is not research. So research is asking a question.

So I actually believe that we can make a very global statement like that but that is not going to solve the problem. Then you put in the specific things that people are questioning about. Is it research or not? But the fundamental thing for me, the big obfuscation is whether it is clinical practice or whether it is research, and I think that is the -- that is the -- you know, open barn door that everybody walks through and that has to be clearly dealt with.

DR. SHAPIRO: That deals with it in the biomedical situation.

DR. COX: Yes.

DR. SHAPIRO: Not in the other situation.

DR. COX: No, but I do believe whether you are a social scientist -- any kind -- that people that

basically do grounded in theory may not say they are testing a hypothesis but they are certainly asking a question.

DR. SHAPIRO: Yes, I think the hard part here, David, is not -- that clearly is a characteristic of research, right, asking and testing an hypothesis and asking a question but there are a lot of other things which we may not consider research that are also asking a question or investigating something. Public health practice is a very good example. They are not just doing it for nothing. They aren't out there doing surveillance practice because it is a recreation or something. They are doing it for a reason and they are looking --

DR. COX: But, Harold, in my view that is not -- that is research.

DR. SHAPIRO: That is research.

DR. COX: Indeed.

DR. SHAPIRO: That is a big issue as to whether we want to include public health practice, quality assessment programs, and all those issues in --

DR. COX: And that is one of the problems because one of the ways that we are defining our definition is we already take -- we already have in the back of our minds things that we want in or we do not

want in, and that is why we are having trouble making this definition.

DR. SHAPIRO: But remember the definition is for purposes of bringing in human subject protections. We are not trying to solve the research problem at large.

DR. COX: No, I understand.

DR. SHAPIRO: Which things, you know, call in all these protections and which do not.

Alta?

PROFESSOR CHARO: But I think again to -- boy, I am really repeating myself so many times today. One of the -- why is it that we want people who are enrolled in research to be the beneficiaries of some kind of third party oversight? Let's ask why. Why are we trying to do this? And the answer is usually about something having to do with some degree of having been turned into a means rather than an end in themselves. Right?

Now, of course, that happens all the time. Right. You get employed to do something and you are certainly a means to your employer's ends and you get money in exchange. So we recognize that this is a familiar phenomenon. So that is part of it, right. That may be a necessary -- it is not sufficient in and

of itself to explain this phenomenon.

The second part, I think, is that the relationship going back to this relational issue, the relationship now is one in which being made into a means, partly or wholly, of somebody else's ends is something that is either not apparent to you or it puts you at some extraordinary level of risk. It is something against which you have difficulty protecting yourself. There is some other element here that is added to it.

It is why, for example, when clinical practice is combined with research you want it to be covered because instead of being solely an end, that is solely, you know, my well-being being the concern of my professional, now that is only one of two very big concerns.

The other one being the pursuit of good science where the systematic nature of the endeavor may not inure to my personal benefit but it inures to the benefit of science.

It is why, though, on the other hand when we are talking about journalism or consumer surveys we are not as concerned about making sure it is covered because there it is very clear that I am absolutely nothing but a means to somebody else's ends and it is

very easy to protect myself. I do not need the assistance of third parties to do so. It is a matter of hanging up the phone and refusing to answer. And it is very apparent what the information is going to be used for.

So I --

PROFESSOR CAPRON: You need a list.

PROFESSOR CHARO: I do not think that we have to really worry about whether we can capture each of the characteristics of the notion of research because that is far broader than what we want to cover here. Right? I think all we want to do is capture a few of the essentials so people have an idea of the general area we are talking about and then use the specifics to identify the specific areas that will be covered, the specific areas that will not be covered, and to recognize there will be gray areas that really merge but try to reduce them instead of starting with a definition that has everybody struggling to interpret it and has nothing but gray area.

MR. HOLTZMAN: Harold?

DR. SHAPIRO: Yes?

MR. HOLTZMAN: Is there anywhere in here do we talk about that relational aspect?

PROFESSOR CHARO: It has come in, it has

gotten dropped out, it has come in, it has gotten dropped out. It has been in the discussion mix but never really gotten --

MR. HOLTZMAN: The only problem with lists of examples -- I mean, if they have any utility, they give you generalizable principles that you should elicit from them. Right? And you should be able to articulate those and that is what I heard Alta just come up with. Beyond anything that one might consider research in terms of intent, generalizable knowledge, yada, yada, it is as a subclass of research that is in play here. All right. And I think we could pull that out into -- I know you do not want to call it a definition but the definition of the research that is in play.

PROFESSOR CHARO: And it helps, also, to put into play why it is that certain areas of social science and humanities work can easily then be excluded. We are no longer claiming that we are trying to pull in everything that is research. We acknowledge that research goes far beyond what we are hoping to cover here.

And it includes the crash dummies and it includes the consumer taste tests and it includes the journalistic interviews.

MR. HOLTZMAN: No, some of it will get turned out, the crash dummies, because it is not a human subjects. Right?

PROFESSOR CHARO: But my point is only being if we recognize that the world of research goes way beyond anything we wanted to contemplate to begin with, then there is no feeling of resistance to the idea that there may be things in the world of social science and humanities that we are also going to throw out because they do not raise the concerns that justify a governmental intervention and third party oversight. Right?

When we focused on the word research because they do, do research, suddenly they all had to be in. And now we recognize that being research is not all it takes to get in. It has to be research and something else.

DR. SHAPIRO: The way the recommendation is currently structured is amenable to this suggestion because it calls -- despite what we are talking about, the recommendation as I read it, I do not recall it now, does not call it a definition of research. It says that job should be accomplished by NOHRO but it should include the following. I mean, that is -- it is not say that we have got the right one, two, three,

which is what, I think, you are referring to. Is that we just have not taken the right tact on trying to give some advice to NOHRO as to what kinds of things should be in and out.

DR. COX: Exactly. But it is a major point, Harold, to say that it is not all research but it is certain types of research and that -- and that really is fundamentally different from the way it is now because it does not make a distinction between -- with the exception of rules it does not make that distinction so I think that is very important.

DR. SHAPIRO: Marjorie and then Alex.

DR. SPEERS: I agree. I mean, I thought I heard Alta saying something more, which was that there are certain types of research and it is that type of research where the relational aspect of it is such that individuals are not used as means or they know that they are a mean. It is not confused with any therapeutic intention or the harm -- the potential risks are very, very low.

And I thought what Alta was saying is that should be excluded from the oversight system. I mean, that is where -- that is what I thought I heard, which is very different from what we have said in this report or the way things are now.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: We may be on to a way of handling this. I am still struggling through the kinds of examples. It seems to me that on the one hand, as the present regulations recognize, there are certain things which are research but which are just not going to go through this oversight process, certain social policy experiments, because our sense is that the balancing of the interests take place through another process, either the Congress or a high level agency official not concerned with human subjects research but concerned with the underlying policy question says that is okay.

But before we sort of say that the real -- the only consideration here is whether or not we are dealing with the question are people likely to be going into this under the impression that they are going to benefit and that is not the case, we ought to recognize that -- I mean, if I sign up for a Phase I drug trial, not of a cancer drug, I mean where we use cancer patients because the drugs are so awful that I guess we think we could not use them. But just an antihistamine or something. And they just say anybody who wants to sign up for this can and all we are doing is studying the toxicity of it to see if it has any biological

effect that is measurable.

I know I am just a means. That is not the issue. So would you say it is not research? No, of course, it is -- just let me finish. So that, I mean -- so I am not disagreeing, Alta, but, you know, which characteristic. I can protect myself. I can withdraw.

Now maybe it is because the people have white coats on that I think none of those things apply and even though it should be obvious to me.

What if it is deception research? What if I am enrolled in research in which I write an essay and people tell me how terrific the essay is but they are really trying to look at the effects of praise on people and the essay is garbage and at the end they say that is all we were doing. We did not actually evaluate your essay. We made you feel good about something which you had no reason --

DR. SHAPIRO: False pretenses.

PROFESSOR CAPRON: False pretenses. And they are psychologists and yet I could have withdrawn and I knew there was no benefit to me. I was just going in to -- and I feel betrayed and I feel lack of confidence now when people tell me something is good. I do not trust people.

What if I am being Lord Humphreys and going

around and observing people's sexual activities and then going to their homes and doing a survey pretending I am doing something else? I mean, I -- there is a whole -- there are on the social science side a catalogue of research protocols which cause some people trouble.

We have not spent much time in this commission talking about them. We seem to have gone into this with a sense that "the biomedical model" does not fit and a lot of people in a lot of fields have been discomforted because they have been forced to have it.

But I do not think that we have yet given the kind of advice that if I were Greg Koski or Secretary Thompson or anybody else who was going to have to sign off on something. I would feel that I had gotten advice that tells me how I ought to change those things.

And I am worried that simply a catalogue of the examples that first come to our mind that ought to be out or conversely ought to be in -- we talked about the plastic surgeons who did two different methods of plastic surgery on the two sides of the face and said they were not doing research because these were both accepted techniques.

Now does our definition fit them? I mean,

that is -- in the catalogue of current things that have been in the press in the last five years is an example of something that should have gone through an IRB and did not because in their own minds they were not having the intent to generate knowledge, facts or whatever. I mean, et cetera, et cetera.

So it was not -- I am just worried that we are not going to -- by this method, we are not going to come up with something which will be as inclusive and exclusive as we think it will be because we really have not catalogued everything.

DR. SHAPIRO: Bernie and Alta?

DR. LO: To me as a doctor this reminds me of debates of trying to find disease or trying to decide who should get a test. I mean there is a sensitivity and specificity problem. Any definition we have is going to be imperfect. It is going to include some things we do not feel comfortable excluding. We are going to exclude some things, we say, gee, we ought to try and get in but to try and tinker with the definition at some point becomes counter productive because it just gets more and more complicated.

I guess -- I think at some level we take our best shot at a definition. We say this is not perfect. Here are some of the things that do not quite fit.

Rather than having, you know, very, very complicated arcane revisions to that version, we prefer to keep it simple. These are things that although technically do not fit in, we really ought to include them and these things that even though they fit in, we do not really think that they really should be in.

Now that is not very elegant. It leads to all kinds of problems but the other thing of trying to keep refining the definition I think -- it will not work eventually. And I think Alex's examples are good examples of where, you know, when you look at it, you say, yes, that ought to be in there but it is not clear how you revise the definition to include those things without either making it very cumbersome or else squeaking in other things that we do not mean to include.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: Well, a few things. I do not know yet if this will work but I still want to see if it can because I know that this is not working so we have got to find some alternative.

I think the list that Marjorie gave was not complete in terms of the factors and so with added factors that either have been mentioned or I am going to mention now one might actually be able to get at

most of your examples. It is not just that risks are low or that people are a means rather than an end or that they are confused.

It also has to do with whether or not they are in, and we are talking now lay people, are in a good position to assess the risks and benefits, which is where your Phase I example, I think, now gets handled because that is exactly the kind of area where it is very difficult for an individual who is not scientifically trained to evaluate the risks and benefits.

And where you are talking anything having to do with deception, by definition they cannot evaluate the risks and benefits because it involves a deception and they do not know what the risks and benefits are going to be. So again that helps to trigger the notion of a third party.

Now your more general concern, I think, I surmise about the kind of basic tension between having a narrow list of covered activities and taking the chance of excluding things that we really would want included versus having a very overly broad list and including things that should not be having an overly bureaucratized basic tension, basic choice.

Let me offer the possibility of a

proceduralist way to get through that thicket. You can start with something narrow, coupled by something that says and we think that the government should consider after a period of two or three years having something that presumes where anything that kind of meets the general definition that is not on these lists that it will now be covered by these rules unless in the intervening time the industries and the people involved in those activities have come forward and explained why it should not be covered.

I mean, you can actually have a rule making process that is like that in which you say we are going to cover things unless people have explained why this should be excluded. It puts the burden on people out there in the field to understand what they are doing and explain why it should not be covered.

PROFESSOR CAPRON: Or issuing a show-cause order of the research.

PROFESSOR CHARO: But my point simply being I recognize this tension between, you know, being over inclusive and bureaucratized versus under inclusive and missing a few people who need protection.

And, I guess, I am beginning to lean in the latter direction of being under inclusive because I recognize that the over inclusive is so over inclusive

that it risks losing credibility within the research community and reduces compliance with the basic rules.

But I recognize that that is a fundamental policy choice to be made.

PROFESSOR CAPRON: The other approach that fits in some ways closer with other things we say is to say to be a little over inclusive and have the IRB be able through its processes to say we do not have to worry about this one because...we do not have to worry about this one because...

DR. SHAPIRO: Arturo and then Bill? Then we are going to have to adjourn.

DR. BRITO: I understand the rationale you have behind this, Alta, and I was finding myself in agreement with a lot of what you have said but I would rather be over inclusive at the onset and come down – an upside down triangle to be less inclusive as you go through.

And Harold said something earlier that he mentioned this is something at a minimum we are giving a definition of research. And I think our report takes care of excluding a lot of individuals or a lot of different types of research as we go through it.

So maybe not in all areas, maybe we could add some other areas where we want to exclude later, but I

would favor having over inclusive definition because for the same reason that we discussed earlier, we discussed before about not including enough about social type research, anthropological type of research.

We tend to focus an awful lot on biomedical models and the perception is that this is always the riskier type of research. This is the type of research that gets people more into trouble, that people may not understand, okay.

But I think on the other hand sometimes people may not understand the risks that are involved from a psychological point of view, from a stigma point of view. So by being overly inclusive I think we take care of that a little bit better unless there are specific examples later we would want to exclude. So I would favor staying with a definition, not this definition but some definition.

DR. SHAPIRO: Bill?

MR. OLDAKER: I think, you know, we have heard what the problem is here and the dynamics of it. I think probably I would lean more towards your direction, Alta. I think my fear always is that if you have -- and this is more from the practical side.

If you have something that lacks definition,

it may cover a lot of things you want to cover in the future, no doubt about that, but I think having people respect it and having people understand what they are trying to do, you are much better off starting with a narrow definition and allowing it to expand as the -- whoever is in charge believes it should expand to cover things.

That model allows things to be taken in incrementally. If you leave it the other way you do create a bureaucratic pattern there because then you basically do not have any direction and no one really knows what is covered and what is not covered with specificity.

DR. SHAPIRO: Okay. Larry, excuse me, I am sorry.

DR. MIIKE: Just contrary to what Bill said. I thought that we had struggled with this before in this report and what we had decided that you have a definition of research but you are going to leave the agency that interprets that, the choice of excluding categories of things, and we even talked about currently the individuals can decide that they are not doing research so they do not even take it so we have built in mechanisms in there that deal with those kinds of situations.

And I would favor what Arturo was saying that -- I mean, no matter what we do, nobody is ever going to be satisfied with the definition that we put down but it is supposed to just sort of show general direction about what we say should be included and then you leave it up to the process to narrow the field and then do exclusions in whatever means you can so that you reduce the regulatory burden.

DR. SHAPIRO: Let me suggest something. We are not going to resolve this here right now but what we will do is we will develop some small finite number of alternatives here and then circulate them around and see what people would like to focus in on because otherwise I do not think we will get to it in our discussion here.

We are also at the time of adjournment.

(Whereupon, at 12:02 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

DR. SHAPIRO: Colleagues, I would like those of you in the room to please assemble so we can get this afternoon's meeting under way.

Colleagues, I would like to begin this afternoon's meeting. Thank you all very much for coming back very close to 1:30 at least and I appreciate that.

We have public comment this afternoon. Dr. Erica Frank, who wants to speak to the commission.

Dr. Frank?

I think there is a single page of testimony. I do not think we had reproduced yet, have we? You will all get copies of this shortly.

DR. MESLIN: I think it is being done.

DR. SHAPIRO: I think it is being done as we speak and thank you very much for being here today. We very much appreciate it and welcome.

Our rules are five minutes.

PUBLIC COMMENT

DR. FRANK: Thank you. I can do one page in five minutes without a problem.

DR. SHAPIRO: That is all right.

DR. FRANK: I am here speaking today as a board member of the American College of Preventive

Medicine and as a board member of Physicians for Social Responsibility, and the boards of both organizations have reviewed the comments that I am going to be making and have approved them, and you will be getting copies of these as well.

There are really two areas that I wanted to address. First, though, I wanted to thank you all for the review that you all did. We believe that this is a very thoughtful and comprehensive review and we would like to thank you for it.

But there are two issues about which we remain concerned and they are about what happens next.

The first of these issues is the imminent sunsetting of the NBAC. Is that how you all pronounce your name?

DR. SHAPIRO: That is good enough.

DR. FRANK: Thank you.

The second issue is you all's mission if you were to continue as we believe that you should into the future.

The first issue concerns the sunsetting of the commission. We believe, of course, that important challenging and new bioethical issues will continue to arise in the United States in essential perpetuity and we believe that there should be a federal agency that

is charged with their oversight. And this agency should go beyond the charge of the OHRP's National Human Research Protections Advisory Committee to include the important and multitudinous nonresearch related bioethical issues. So we hope that that will be enacted.

Regarding sunsetting, the AMA requested the permanent establishment of such a broad entity at the December 2000 meeting, and I will not read you the resolutions but this was a resolution that the American College of Preventive Medicine and the Association of Public Health Physicians put it and it was passed without much dissent at the AMA. So many organizations hope that you all will continue in some form in the future and not just with issues related to issues but with issues that are broader than research.

The second issue is the mission of such an organization were you to continue and we believe that there are four major principles that should be considered, adopted and promulgated by such a permanent body.

The first two principles apply to all of medicine.

The first one is volunteerism, that participation in research and treatment should be

voluntary and we would like to go beyond that simple concept to expand that the concept of volunteerism is of course very broad and extends beyond subjects in a controlled experiment.

Volunteerism specifically to us also means informed consent about reversibility. The effects of most experimental drugs can be measured in hours and days and generally only affect individual subjects consuming the drug but some interventions such as altering the human genome may reverberate throughout our species' future. We hope that a future commission would specifically consider the ethics of involuntary, irreversible changes being imposed on future generations.

The second principle that we hope would be considered that applies to all of medicine is the precautionary principle and this is a fundamental principle that is used by physicians for social responsibility in much of our advocacy and work, and is also adopted by the American College of Preventive Medicine for the purposes of this statement.

We hope that the precautionary principle will always be exercised and this means that when it is the best available assessment given the current evidence or lack thereof that the potential for harm has a

reasonable chance of exceeding the potential for good, that concern for harm will always take precedence, and the process, research or treatment will not take place.

The third and fourth principles, the final principles that we hope that you all will consider adopting for future -- for a future mission would apply to work funded by taxpayer funds. And again I suppose I must even apologize, these principles must all seem rather rudimentary to this group but we hope that our endorsement of them will be useful to you and supportive of your work.

These last two principles are the greatest net societal good that were determinable that research, preventive measures and treatments that have the greatest ratio of benefits to costs for the greatest number of Americans should receive the greatest portion of taxpayer dollars, that there would be a deliberate and rational approach to determining what -- where funding should go.

And the last concept and one that I am sure that you all have spent enormous amounts of time considering is that of equity, which is that participation -- that subjects participating in taxpayer funded research should receive equivalent opportunities and protections regardless of their

personal characteristics. And, in particular, that subject protections for federally funded domestic research should also be applied in federally funded nondomestic research.

Again we thank you for your work and we hope that these comments are useful to you all.

DR. SHAPIRO: Thank you very much. Let's just see if there are any questions from any members of the commission on any of these issues that you raised.

Alta?

PROFESSOR CHARO: In any way do you see anything we have done to date as deviating from these principles that you are advocating?

DR. FRANK: No. We hope that these concepts are useful to you in advocating for being able to continue your good work.

DR. SHAPIRO: I am sorry. Is there another question? I have another question but let's see if there are other questions first.

Yes?

DR. LEVINSON: Just that you said that you thought the mission of this group or its following group should be broadened beyond research. Do you have any specific examples which you think it should consider?

DR. FRANK: Well, just that there are many areas in medicine that have -- and you all can certainly describe those better than could I that have important bioethical implications and my understanding is that all that has been institutionalized in terms of a group to follow you all is a group addressing research. And there are areas around practice, in particular I guess that is the most obvious corollary to research, around practice of medicine, as well as funding that would affect both research and practice, that to my understanding that there is not a plan to institutionalize a commission to regulate or to recommend -- to make recommendations around those areas.

DR. LEVINSON: Thank you.

DR. SHAPIRO: Could I just ask you a question regarding this statement around equity and trying to understand what is meant that subjects should receive equivalent opportunities regardless of their personal characteristics. You also have in there protections. I am interested in the opportunities part. What -- I just want to clarify what you have in mind.

DR. FRANK: It is an extrapolation from the efforts that have taken place recently to make sure that women and the elderly and children and folks with

various sexual orientations all have the opportunity to be included.

DR. SHAPIRO: I see. Okay. Thank you very much. I just wanted to make sure I understood that. Any other questions?

Well, let me thank you very much for coming today. We very much appreciate you taking the time and your colleagues for helping to prepare the statement so please pass our thanks on to them.

DR. FRANK: Thank you.

DR. SHAPIRO: Thank you very much.

Is there anyone else here today who wishes to speak to the commission?

Okay. Thank you very much.

Let's then return to our work. We had been considering issues that came up in Chapter 2 and the first issue that we discussed was really surrounding Recommendation 2.4, which some interpreted as a definition of research, others found other difficulties with that.

And I would like now -- I want to in just a moment go on to other issues because we do have to now take advantage of your comments you made and articulate something a little different.

As I understood the comments, and as I think

about 2.4 or what might be one or two recommendations that might swirl around what is currently 2.4, the challenge is not so much define the definition of research. That is probably a very hard thing to do as everybody indicated this morning. But to try to define what it is that ought to be subject to third party oversight because there is all kinds of research sort of not relevant here so it is really human subjects research that requires third party oversight and it is the intersection of those two concepts that needs some attention and we will give it to it along the lines that you talked about this morning.

And it may be that we need the companion recommendation to go with 2.4 or at least somewhere in here which really calls upon NOHRO also to think about a great deal more procedural flexibility than has been exhibited up to now having to do with such issues of what the presumption should be regarding noninvasive social science research and so on.

And we will attempt to construct something along that line and we will pass -- I do not know if we will do it before we leave here in the next day or so but we will certainly do it in the next few days and pass it on and see how the commissioners react to that.

So let's now consider other issues that come

to mind in Chapter 2.

Any other issues anybody would like to raise?

Bette?

DISCUSSION OF DRAFT REPORT: CHAPTER 2 (Cont.)

MS. KRAMER: Looking a the text on identifiable --

DR. SHAPIRO: Yes.

MS. KRAMER: It is on page -- begins on page 42. In an earlier draft, actually the draft that is dated November 22nd, 2000, there was -- there was text included in that section that has since been dropped and it relates primarily to the use of coded data. And I wonder -- I do not remember why it was that it was dropped. I was curious why it was dropped and I have the sheet in front of me and it -- there is some of the language that relates to again one of these problem -- one of these problem protocols.

One of the protocols at the twin registry at VCU that they are having -- that has become a problem. It says when the coded data -- this is the November 22 language.

"When the coded data are used by recipient investigators, the recipient investigators are not engaged in research involving human participants."

Examples are -- and it goes on to give examples. They have -- they have gotten the -- in the twin registry they have, they received -- their research -- researcher A recorded the material and coded it, and then sent it all on to them. So they are receiving coded data which by our definition is identifiable and they have got to go out and do the requisite things. It turns out that researcher A is the Swedish Twin Registry. All the information comes from Sweden and yet they are subject to -- they are subject to the same rules.

I looked back at this language and it looked like a reasonable interpretation of this language would have eliminated that need and I do not know -- I might be reading it wrong but I wondered why this particular language was dropped from the current draft.

DR. SHAPIRO: I have a memory about this but, I do not know, Marjorie, do you want to respond to that first?

DR. SPEERS: I believe that the reason it was dropped is that basically the commission or commissioners thought that if data are coded data are identifiable and that at the same time that they are identifiable there is a range in identifiability and that that should be handled by the IRB. So that in

this particular situation where these data are identifiable an IRB would probably very quickly review something like that because the potential to identify individuals in this situation that you are describing where the identifiers are in Sweden and not here, and there are probably country laws that would even protect against the release of that identifiable information, would make the review of that project a fairly simple review because you could assume that there are adequate confidentiality protections in place.

But I think that the commissioners were uncomfortable saying coded data are identifiable but there are some situations in which they can be treated as if they were not identifiable. That is my recollection of the discussion.

DR. SHAPIRO: I think that is correct. That was specifically discussed. I mean, not this example obviously but that issue.

Eric?

DR. CASSELL: This must have been discussed and I just do not know about it. Suppose we set up an experiment where there are four -- we set it up so there are four participants on a data stream. We set it up so that the data is coming out and being averaged from the four of them all together. They are all

exposed to the same stimulus but they are at risk. Are they not research participants even though the data that comes out cannot be connected to them?

DR. SHAPIRO: I need a description of the experiment again. I did not quite get it.

DR. CASSELL: Well, I mean, there is -- it seems to me two things are being talked about. If data is being used which can be identified then that is human subject research no matter where the -- when the data was collected or not. That is like the human biological material. But suppose we set up this experiment so that a data stream is provided that averages the data coming off these people's skin galvinometry, for example. And they are all exposed to the same thing. We do not know whose is what. It is only going to be one thing and yet they are put at risk, are they not research subject participants?

DR. SHAPIRO: Alta?

DR. CASSELL: Well, they are put at risk because they might be embarrassed by the questions they are being asked to produce this or by the fact that needles are implanted to get this galvinometry or whatever.

PROFESSOR CHARO: Eric, I think that there are two things here, both of which have already been

handled in different places, I think. The first is Bette's example, which was handled under the HBM report, and the problem with the sentence in the November 22nd version is that it contradicted the HBM report. And unless we were going to redo the HBM report we needed to take it out because we had contemplated this dilemma and had proposed a solution.

Your example, Eric, seems to be one in which you are actually sticking needles in people's hands.

DR. CASSELL: I cannot hear that. Say it again.

PROFESSOR CHARO: It sounds to me like in your example you are sticking needles in people's hands. That sounds to me like they are human subjects and you would have to consent them.

DR. CASSELL: I do not understand that.

PROFESSOR CHARO: Well, maybe I do not understand your example. Didn't you say you were going to stick needles in people's hands?

DR. CASSELL: Yes, let's do it that way. Let's get our data that way by putting needles in them.

PROFESSOR CHARO: Don't you usually have to get consent from somebody before you stick a needle in their hand?

DR. CASSELL: Yes, they are participants. The

point -- whether a study is human research should not be simply the data. The data -- if -- what the point of this really is, is that only data alone can be human subject research if that data is identifiable.

PROFESSOR CHARO: That is correct. That is the HBM report, isn't it?

DR. CASSELL: That is right. That is exactly right. If the decision point for whether a study is human research should be whether the data are identifiable. No, it is whether the subject is identifiable. And if there is a human subject, even if the data is collected in a way the subject might be put at risk while the data is being collected, that is not the HBM report. In the HBM report that is all long gone. We are now talking about tissue. Most of our participants, we hope, are not just tissues though doctors have been known to treat people that way.

DR. SHAPIRO: I think that is right.

Other comments regarding issues in Chapter 2?

I am sorry, Alta, excuse me.

PROFESSOR CHARO: I am sorry. It is just a minor point.

DR. SHAPIRO: To my left is always -- I do not see so easy.

PROFESSOR CHARO: I like to sit on people's left.

DR. SHAPIRO: To say nothing as to my right.

(Laughter.)

PROFESSOR CHARO: It is just a minor point and it comes up on page 11 in which we discuss accountability. Along with the notion of accountability it would be nice to use this opportunity to emphasize a related concept of responsibility. No place in one and two do we get a chance to emphasize that we think that the primary responsibility lies in the hands of the investigators and the review boards to maintain an ethical stance in their research.

And that is something that we have heard from people around the table as well as people in the field as being important because it decreases the chance this is seen as a top down governmental program and increases the chance that it is seen as something which is about professional self-regulation supplemented by government oversight.

So this looked to me like a spot where one might do that.

DR. SHAPIRO: Okay. Thank you very much. That is helpful and I think we should do something in that area.

Other issues?

Again, I want to -- those of you who through e-mail or otherwise have provided suggestions regarding text, those are all being incorporated in. Many of Bernie's suggestions and so on. Other people have made suggestions. We are incorporating them in the text. In the next text you will see -- in the next version you see will have all those inside.

Okay. I do not want to rush us and I do not want to delay us so again I want to ask if there is any other issues that arise.

DR. MESLIN: I guess --

DR. SHAPIRO: Yes?

DR. MESLIN: Just for the record, there is a document that is being handed out. This was to have been inserted during the public comment period. It is a memo comment from Bill Freeman that was asked to be presented at public comment so at least it is in your hands to be read by you.

DR. SHAPIRO: Let me raise a question for those who know more about the Office of Government Ethics than I know. At least one commissioner has raised the issue, I do not now remember who it is, that this may not be a very good analogy to use because, after all, the suggestion was it is not clear the

benefits outweigh the costs in establishing this office.

I am just looking for information from people who know more about it than I do as to whether this is -- I mean, our recommendations do not depend on that office. We are doing it for other reasons, not because that office is a huge success but because we feel there are other reasons to locate the office as an independent unit but I just -- so this is a small subquestion as to whether people who know about this think that that has been a very useful thing in the federal government or whether on balance it is, you know, more trouble than it is worth.

Has anybody here -- Bill, do you have any experience in that?

MR. OLDAKER: With the OGE when you are talking about financial matters, I guess, and disclosure by various government employees, I think actually, it has been very useful in that it has centralized the responsibility, which was very dispersed before and it basically was agency oriented, and set up standards so that people could (a) disclose but (b) on the other side so that the public had a place to go to, to make a determination and to get information.

And so it served both sides. It served for the government officials. It gave them kind of a touchstone to know what they had to do when they filed their reports. Now many of the agencies like the State Department have stricter rules and people -- they have to also go through that, their ethics officer at that agency, and file a report, the publicly disclosed report with the Office of Government Ethics.

I think it has worked as well as any system like this can work but it -- one of the things is it is creating an efficiency in the government where, historically, there are great inefficiencies in alot of this regulation. That is because in this area there are great inefficiencies because there are so many regulators.

And as far as the cost, my guess is there is a cost of regulation in that people have to more thoroughly comply with the regulations. They may not have in the past so there probably is some cost that goes along with it.

DR. SHAPIRO: Well, cost is fine as long as there are benefits that are associated with it.

MR. OLDAKER: Right.

DR. SHAPIRO: I did not mean to do this with zero cost.

Anything else to come up in Chapter?

DR. BRITO: Harold?

DR. SHAPIRO: Yes, I am sorry, Arturo.

DR. BRITO: I had a concern about just a simple sentence in one of the paragraphs in Chapter 2 that refers to OHRP. What I think would be useful is some distinction about what NOHRO -- how NOHRO or however we are going to say it -- it would be different -- what the role would differ from OHRP and I think that is important because the reader -- it almost comes across that they have -- they maintain similar roles and that is not the intention I do not think, right. So just some -- just make sure we have some language in there. I am not sure what that language would be.

DR. SHAPIRO: Okay. Any other comments or suggestions?

Okay. Sort of a going, going, gone thing. We will come back to this when we have some new language on the issues that have been of concern.

Let's now go to Chapter 3. Let me begin by asking -- I should have done this before. I apologize, Marjorie -- asking you if you have anything you want to say about Chapter 3.

DISCUSSION OF DRAFT REPORT: CHAPTER 3

DR. SPEERS: I think there are -- I mean, my

comments are based on, you know, what were perceived from the public comments on the draft. There are two recommendations in this chapter that I would like us to consider.

One is Recommendation 3.2, which relates to the standard for determining minimal risk. And the issue that came up in the public comments with regard to that was whether the standards should be the general population or the healthy population, or whether the standard should fluctuate based on the population that is being targeted for the study.

So I think that you should -- there should be some discussion about what standards you want if you want a standard.

Bernie brought up a good comment related to minimal risk which was, in effect, we say we have -- that we are proposing an absolute standard but, in fact, it is relative, relative in the opposite direction. That is to say, we set it as the general population and then, if individuals who are vulnerable are going to participate in the research, then we have to judge it again and determine if it is still a minimal risk study or not and that that is a -- potentially a relative standard because it may be more than minimal risk if vulnerable populations are

involved. So I think there should be some discussion about that recommendation.

The other recommendation is what was the old 3.10 or the new 3.11 and it relates -- it is the issue of among those individuals who are vulnerable, if the study involves more than minimal risk, if the research components involve more than minimal risk, and individuals are unable to give consent, then we recommend that that type of research go to a national review board or a specially accredited IRB for review and, hopefully, that some guidance would be -- would follow after that type of research had been reviewed and we were familiar with it or the national board was familiar with it.

In that recommendation when we break that down and look at the particular comments that we received on it, virtually all of those comments deal with the recommendation of some type of national review or additional, review and among those comments, I think again, they broke out into two categories. Those who are not opposed to additional review or national review but have concerns that there will be unnecessary delay and then those who are opposed to it who feel that local IRBs should review that type of research.

I think that may be revisiting some of the

discussion or issues that came up when you were working on the Capacity Report. But of the recommendations, the old 3.10, the new 3.11 received -- one of them -- was one of the three recommendations to receive the most comments so I would like to have some discussion on that recommendation.

DR. SHAPIRO: Okay. Well, let's go to -- of course, there may be other issues that will come up here but let's go to Recommendation 3.2, which has to do with defining minimal risk or giving some way to think about minimal risk. Well, I am not going to repeat what Marjorie said, just ask people how they feel about the current status of 3.2.

DR. CASSELL: Then we will go back to 3.1?

DR. SHAPIRO: Oh, yes. We will go back to -- we definitely have to do 3.1 because I do not think it is adequate the way it stands. That definitely has to be changed in my view. Let's just go to 3.2 first and then we will go to 3.1. I guess there is a new 3.1 --

DR. MESLIN: He meant 3.1.

DR. SPEERS: He said 3.1.

DR. SHAPIRO: Or 3.1. Any one of the others we will go back to.

DR. SPEERS: Do you want to just go in order?

DR. SHAPIRO: No, let's take the two that you

focused on first because a lot of public comments came in on those. So let's do 3.2. Would people like to make changes?

Steve?

MR. HOLTZMAN: Well, I guess the question I have about 3.2 is whether we are in agreement on what we want versus whether we are getting hung up and if that is true are we just getting hung up on uses of relative versus absolute. So my sense of what we were trying to do and I think we agreed to is look at the general population, if it is more risky than it would be for the general population, it is more than minimal risk.

And if it is less risky but it is less risky only because of the condition of the individual involved, e.g. who gets involved -- someone who is normal often gets stuck with needles and that -- that is not a good enough reason so that is what Bernie's concern was.

And then we would also then have room in that to deal with the kind of thing Freeman is talking about which says that given that you are already in that person's body for a procedure it is not -- it is more -- you are contextualized and that -- you are contextualized and it is still relative to the general

population. If it is the general population who has already got their abdomen opened it up, it is no additional risk to just take a little bit more sample. I think that is what we said. Whether you use relative or absolute, is there any disagreement with that?

DR. SHAPIRO: That was the way I thought about it and I think the relative or absolute we ought to put aside. Obviously absolute is not the right way to describe that because we do allow for changes so that issue we will have to take care of but I do not think we disagree on that issue. Let's not get held up on that. But it is my understanding that is what 3.2 does.

MR. HOLTZMAN: That is how I read 3.2.

DR. SHAPIRO: Yes, right. If it does not say that then we have a problem.

Yes?

PROFESSOR CHARO: Yes. Would you prefer comments about the actual language to be done at the table or handed in?

DR. SHAPIRO: No, if it is not a substantive issue why don't you just -- you know, use your judgment, Alta. I mean, whatever you would like but, I mean, I think if it can be handled simply as a matter

of simple language and not a matter of substance then we -- if you just hand it in, that is a lot easier for us to handle.

PROFESSOR CHARO: Well, it is a dramatic rewrite but it is not aimed at trying to change the substance. It is just a rewrite.

DR. SHAPIRO: Okay. Well, why don't you --

PROFESSOR CHARO: I will just hand it in.

DR. SHAPIRO: -- hand it in and we can share it with everybody but it would be hard for us to deal with it at the table --

PROFESSOR CHARO: That is fine.

DR. SHAPIRO: -- in any effective way since we do not have copies yet.

DR. COX: I think this illustration, though, of the absolute versus relative, is a really excellent illustration of why having the central office might be useful because no matter how much you write things down when that comes up, the central office can make sort of statements about this. We are not going to be able to put every single one of these in our report. This one we can put in because it was from public comment but these will come up all the time.

DR. SHAPIRO: Right. Okay.

Any other comments on 3.2? I think, Marjorie,

you found out that we had a substantive agreement on what we are trying to get accomplished here and we will look at the alternative language.

DR. COX: Which is good news.

DR. SHAPIRO: Okay. Why don't we go then to 3.11 and then we will come back and deal with other issues. Turn to 3.11. I do not know which page it is on. I am actually working on the -- 3.11 is changed in a number of ways. In fact, I have been going through -- going back and forth with Marjorie and Eric over the last four or five days. We have had a number of different versions of it and I would like to pass around for your consideration a somewhat different version and maybe give you a few minutes to just read that. This is 3.11.

And it is -- the version that is coming around is not meant to change what I understood to be the substantive nature of this but just clarified it for me in a number of ways.

For one thing the original version, at least that I was working with, put the decision on whether certain components were greater than minimal risk and I have changed that in here to say if any component is more than minimal risk regardless of which component it came from, whether it was in the research only

component or the clinical only component, the issue was if any component is more than minimal risk this stuff starts happening.

That was really -- and the other was just clarifying language. That was really the only substantive change I believe that I made.

There are other issues we may want to discuss in a few moments on 3.11 but that is the only way this was changed. It was really just to simplify it and clarify an issue.

PROFESSOR CHARO: It actually works very well.

DR. MIIKE: There is no section 3 in the revised version.

DR. SHAPIRO: There is no section 3 and let me remind myself what section 3 was.

MS. KRAMER: That was a version that was two versions ago.

DR. MIIKE: I am looking at the one that is --

MS. KRAMER: Right, but then there was another.

(Simultaneous discussion.)

PROFESSOR CAPRON: Is this the same as the e-mail?

(Simultaneous discussion.)

DR. SHAPIRO: That one, that is right. Again there was only one substantive change I made in redrafting this. It is not a -- it could be the same.

(Simultaneous discussion.)

DR. SHAPIRO: The one substantive change I made was to focus on any component about minimal risk or not. Everything else is just some, I thought, language that made it somewhat clearer or it may or may not be true but that is how I thought about it.

DR. SPEERS: There are three -- unfortunately, now there are three versions of 3.11. There is the 3.11 that is in your briefing book. There is an edited version of 3.11 that was sent out by e-mail and it is -- if you are using this handout with the table form that is in there, and then there is the one that Harold has -- that we just passed out now for Harold.

PROFESSOR CAPRON: One more demonstration that this commission cannot get by without scholar and biblical hermeneutics. I mean someone --

DR. SHAPIRO: I am glad you are here with us, Alex.

(Laughter.)

PROFESSOR CAPRON: And Jim Childress is the closest one we have and he is not here.

DR. SHAPIRO: We will put him on the phone if

we can get him.

PROFESSOR CHARO: I would like to put in an endorsement for the latest version of 3.11 that was just distributed at the table. It seems to be clear, chronological in its review process, and it makes it very easy to understand what are we supposed to do and when. And for the people who are criticizing it, I suspect they are exactly the same people that criticized the capacity report, and I would like to urge us not to revisit the capacity report but to continue to endorse its conclusions there and here.

DR. SHAPIRO: Well, the particular issue that Marjorie and I think Alta is also referring to now has to do with, I think, when research involves more than minimal risk, what happens and when it has to, in fact, go to something beyond the local IRB, which is more than minimal risk, unable to give consent category.

Steve?

MR. HOLTZMAN: And just for clarification without revisiting the capacity report, are children clearly unable to give informed consent in the sense of what has just been handed out? And if so, then it is not simply revisiting the capacity report, it is rather agreeing not to revisit the capacity report. We are also agreeing to the extension of the logic of the

capacity report.

PROFESSOR CHARO: Oops.

DR. SHAPIRO: Well, I think there is a whole series of issues with children which, in fact, are not dealt with in this report, which this is only one. That has to be dealt with over time.

Yes, Larry?

DR. MIIKE: Just a minor point. In your revision, maybe it was just a short cut but 2(b) does not say anything about as long as there -- a legally authorized representative has approved just to be consistent between --

DR. SHAPIRO: I see. It would need that plus a review.

DR. MIIKE: Yes.

DR. SHAPIRO: I understand what you are saying.

PROFESSOR CHARO: A question?

DR. SHAPIRO: Yes.

PROFESSOR CHARO: I thought I remembered but I could be wrong, I thought I remembered an earlier discussion in which there was an agreement to not have this report cover special concerns about children.

DR. SHAPIRO: That is correct.

PROFESSOR CHARO: Because it was going to take

a full scale report in and of itself.

DR. SHAPIRO: That is correct. I think there is something in the report that says that.

PROFESSOR CHARO: So that would be -- this would be a moment then in the text to reiterate again, perhaps for clarity, that the report is not handling the question of research with children and focusing only on adult incompetence.

DR. SHAPIRO: Bernie?

DR. LO: Yes. I appreciate the desire not to revisit the capacity report. My concern is the example given in the text of research on kids with leukemia. It is probably one of the big success stories of human research and if we are not going to deal with children, let's change the example because I think it is so counter intuitive to what many of all stripes would say is the type of research that we do not want to send to a national review body because we do not see what is to be gained and it is going to slow down research in an area that has already proven to be of incredible benefit to kids who, when no research was being done, were doomed to a death sentence.

So I think that, you know, there is this tension between not wanting to let things slip by that review but if you do not do the research, the people

who you do not do research on will never get the benefits of knowing what works and what does not. And peds is a good example where a lot of investigators, against a lot of odds, said, "Let's do research." People said, "You cannot and you are torturing the kid," and now it is a curable disease in 90 some percent of cancers.

So let's at least change the example.

DR. SHAPIRO: I think that is absolutely right.

Other comments? Alex?

PROFESSOR CAPRON: What happens in the category between A and B? There seems to be a lacuna there. You have on the one hand those who are able and those who are clearly unable. What about those who are possibly --

PROFESSOR CHARO: Unclearly unable.

PROFESSOR CAPRON: May be unable.

DR. SHAPIRO: No, that bothered me, too.

PROFESSOR CAPRON: After all, we went at great lengths in the capacity report to address that maybe category, and one of the first issues to be decided is where a particular subject or group of subjects falls as to that research and the whole notion of capacity related to a particular type of intervention with a

particular set of risks.

PROFESSOR BACKLAR: Particularly the issue of people who do have capacity at point -- temporal point A but may, in fact, lose capacity during the progress of the research.

DR. SHAPIRO: I am glad you raised that point because when I reread it this morning that bothered me quite a bit also.

PROFESSOR CAPRON: Do we want to see this as three categories or just as two, in which case it is the adverb "clearly" that we do not want here.

DR. SHAPIRO: Maybe or something.

Steve?

MR. HOLTZMAN: You know, if we go back to where this starts in the report, we are trying to get away from the classification of individual groups and we are going to give a conceptual basis for vulnerability. So, not surprisingly, the first draft of this talked about what you could and could not do with respect to people who were vulnerable, right, where vulnerable has to do with whether or not their consent can be genuine.

So now having moved off of that, because it seemed to throw the net potentially too widely, question mark, are we now getting ourselves into these

deep waters, which we were trying to find a way out of by trying to give a conceptual framework for vulnerability?

I am asking first if that is what is happening to us here and then we can figure -- if not, they do not have to pilot out of it.

DR. SHAPIRO: Well, speaking for myself, I did not think about it that way. That is not the process that my own thinking went through. I cannot speak for anyone else.

But I wanted -- as I looked at this, I recognized the problem that Alex raised and we have to resolve that. But it seemed to me we wanted some indication of how we thought this might be handled and that is as far as my thinking went.

PROFESSOR BACKLAR: But it does not seem to me that we are identifying populations here. We are still identifying individuals and that is the whole point of the development of that model of vulnerability, that we are looking at individual vulnerability, not population vulnerability. And so I think that the issue is not --

DR. SHAPIRO: Alex?

PROFESSOR BACKLAR: -- not the one that you thought.

DR. SHAPIRO: Excuse me, I am sorry.

PROFESSOR BACKLAR: But --

PROFESSOR CAPRON: Go ahead.

DR. SHAPIRO: I did not -- I thought you were through. I am sorry.

PROFESSOR BACKLAR: But I think the point that Alex made before is extremely important and we have to find some way out of it and it may be that taking a -- it is not just that -- even taking clearly away that you are saying unable to get consent. We are making that a category and we may have individuals who can give consent now but not later.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: It seems to me that when we are thinking of this as an IRB process, the IRB is not looking at individuals. They are looking at a group of prospective participants about whom some things are known. This is research on the kind of condition which may interfere with individuals being able to consent now or at some point during the research process.

But the IRB is not meeting Bob and Sue and Ted and Alice, and making judgments. Somebody may make judgments about them but the question as to whether or not the research should get administrative review or local IRB review or local IRB review and something more is not something which is going to depend upon

knowledge of any individual.

And so we have got to be clear that we are in a way talking about a group of people who have potential vulnerabilities, right? Is that not correct?

So when you get down to getting consent from any one person, someone who is in that category may be judged by someone, probably better not just the researcher herself but somebody else as well as this person actually is able to evaluate all the risks here and make a consent that would be valid and even if it is more than minimal research they could consent to it.

This person cannot do that and, therefore, some of these other things have to be triggered. The IRB will have come before all that. I mean, they are going to have to decide about that process and whether it will be adequate. So I am a little concerned that we not think that we have avoided this problem by -- well, we are not talking about vulnerabilities in the old way. Well, we are not talking about in the old way with everybody in mental institutions, every prisoner, every child. Of course, we are not talking about children at all. But I mean everybody in huge groups.

But if you are doing this kind of research with --

PROFESSOR BACKLAR: People with Alzheimer's.

PROFESSOR CAPRON: -- people with Alzheimer's you are going to be -- you are going to have to say yes as it -- there are potential vulnerabilities here. We are going to have to have some process for saying is it minimal risk or more than minimal risk and then, within that, can this individual consent but the IRB is not going to be involved with that process. They are going to have to have made their decisions before you get to that point.

DR. SHAPIRO: A couple of people want to speak but first there is Larry and then Eric.

DR. MIIKE: Just looking again at this recommendation, what Steve said just struck a note, which is that this is a section about vulnerabilities, talking about socially vulnerable, economically vulnerable, and yet this recommendation is really not about all of those people even though it is listed as dealing with vulnerabilities.

This is more about people with impaired capacity so I am looking at this and I say if I had no vulnerability -- if I were a Protestant White male in America, middle-class, et cetera, this could apply to

me if I had no capacity to consent. So this is really not -- and so I am thinking we have already addressed this issue in the capacity report. So why do we need this in this report?

DR. SHAPIRO: Okay. I want to let other people speak. I have my own answer to this but let's get other people to speak. Eric, then Steve, then David.

DR. CASSELL: I have some feeling about that but I also -- again this may have been argued out to death but I -- the dividing of research into the parts that have greater than and the parts that are really quite safe. It is either research or it is not and my concern is somebody designs a study and in that study they are about to give a drug which, in and of itself, is not risky but to find out whether the drug does any more they do things that do have greater than minimal risk as the example given but you are right about leaving behind childhood leukemia.

Now if it is the proper way to do that study, it is part of the study. There would not be conceivably, if that is the proper way to do the study, any study in which only the drug is given. And there would not be a study in which only the risky part was done. The study is the study.

We would like investigators to come away understanding that they must be very careful about their studies but we want them to understand if they do not modify their study in order to meet a minimal risk standard, to modify their study only to the extent that it provides -- it does the job it was meant to do. This sort of implies that you can do that, that you can move your study around a little bit. I see no advantage of it at this time.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Two things. The first to Larry. I think if we look at the list of vulnerabilities, we do have capacity related cognitive disabilities.

DR. MIIKE: No, I understand. What I am saying is this applies to all vulnerabilities.

MR. HOLTZMAN: Right.

DR. MIIKE: Which really does apply to the capacity.

MR. HOLTZMAN: So, Alex, speaking about how you were framing it, so suppose my population, I go to the IRB, I want to perform a study, which is more than minimal risk on patients with Alzheimer's. If I include, as an exclusion criteria for the subjects, all right, or inclusion/exclusion, I will only include

those capable of consenting, then I would not need the national review. Whereas if I throw the bucket more widely then I would and then the way it would play itself out if the local IRB then approved it because I excluded those unable to consent, if I then came upon that individual I would not include them.

PROFESSOR CAPRON: Or the IRB might say to you we want an independent mechanism to screen people and make sure they are in category A or in category B.

MR. HOLTZMAN: Okay. That is the way it would play out. Okay.

DR. SHAPIRO: Okay. Trish, you are on the list.

David?

DR. COX: Yes. It is in this middle ground between those people that clearly can consent and those that cannot. So it is a point of clarification for myself because as I was thinking about that operationally along the lines that Steve was just doing it, so for me -- this is just a personal thing -- if I was in doubt, okay, of whether a person could or could not, I would like to err on the side that they could not.

Now is there a consensus among the commission about where we are on that because if people -- if

there is a consensus about that then it is really straight forward what you do with the people in the middle. If there is not a consensus about it, then how we deal with it is going to be extremely difficult.

DR. SHAPIRO: Well, I want -- Trish wants to speak on this issue. It is my own sense that it was unfortunate to use words like “clearly” unable. It created a class unnecessarily from the way I look at this. If you take out the word "clearly" I understand this a lot better and I do not know why they used that word. They used that word -- now that I think about it.

PROFESSOR BACKLAR: Everyone wants to say maybe.

DR. SHAPIRO: Yes.

(Simultaneous discussion.)

DR. COX: That was -- yes, that was sort of my point because unless somebody can really do it, I would like to be under the presumption --

DR. SHAPIRO: But I have a series of comments I want to make on this but I want to let Trish be first.

PROFESSOR BACKLAR: It is actually not terribly important except that I think that it is important to understand that we can still use these

types of vulnerability, and that would cover those who can consent and those who may not, because they are vulnerable to cognitive difficulties.

DR. SHAPIRO: I think I want to raise a general issue here which has bothered me every time I have read through this section on vulnerabilities. I mean, I do like the new model, if I could call it that, and so on but -- and we all agree and have said and we have heard in public comments again today that, you know, all groups should be included. We do not want -- we want to give people equitable access to trials, et cetera, et cetera, for all the reasons that we understand.

However, it is true that there are -- some people have sort of brought up one way or another here -- incentives not to do that because as soon as you get to that you have got another barrier to overcome. And I do not know any way around that.

Now to give examples like you are studying -- I guess the example given here was Alzheimer's patients. That is already a group which one has to obviously be very thoughtful and careful with. But supposingly you are not selecting any particular target group like that but you are trying to test a drug on the population in general. You are very likely to get

a vulnerable person in there especially with our new definition of vulnerable. Right? You can be vulnerable as Larry said for a large variety of reasons.

And any time that vulnerability comes in under -- especially if you are unable to give consent and so on, you stand a chance of having to get a higher hurdle. I do not know what to do about this issue in my own mind frankly. The fact that you do have that incentive. There is every incentive for someone who comes up with a study and somebody who comes through as a possible potential participant. You look at that and say this vulnerability sort of caused me some difficulty but we get some other participants here.

Alta?

PROFESSOR CHARO: Well, first, I think that there is a legitimate difference -- I think there is a legitimate reason to differentiate between the many kinds of factors that we have identified as making some people vulnerable and the specific phenomenon of impaired decision making because impaired decision making is at the essence of being able to protect yourself. The whole notion of autonomy and being able to, you know, refuse and to consent, a lot of this is about the ability of a person to say I can protect

myself by saying no. It is at the core of it.

Certainly other aspects of people's relationships can make that difficult to do. I can be in a situation where it is difficult to exercise autonomy. That is why we are calling those situations ones that raise concerns about vulnerability but none of them are essential as the actual intrinsic inability to make a decision. I do think that you can distinguish these things and treat them separately.

Second, the ones that have to do with capacity to make decisions are the only ones that raise the issue of secondary surrogate decision makers, which is another reason to separate this out. So it does seem to me that we can start by separating them and then next, yes, we can pick up people with a variety of vulnerabilities but I think the concern we have primarily is research that is recruiting a population that we can predict will be vulnerable in the context of this research.

All right. It is not that all research runs the risk of picking up somebody who turns out to vulnerable. It is that some research is designed deliberately to work with a population which for this research protocol is somewhat vulnerable. Right?

Therefore, what we might want to say is

something as simple as when a research protocol proposes to study a population that is made up of vulnerable individuals for that research, vulnerable in that context, then the protocol must be reviewed by the entire IRB before it is approved. We do not want to give it a fast pass. It needs to get a complete look and that is all that has to be said there.

There is no issue about secondary decision makers and the limits of their discretion and the need to go to national boards or any of that.

Next, totally separately what Harold drafted with the word "clearly" deleted, right, and just saying able and unable, I think, would no longer be about vulnerable individuals but it would be specifically about individuals with impaired -- you know, impaired capacity to make decisions and it would cross reference to the capacity report for further details about how to assess the capacity of the individuals, et cetera, et cetera.

But that way I think we can tease apart these procedural sequelae of certain kinds of preliminary findings about the nature of the vulnerability.

DR. SHAPIRO: Steve and then Alex.

MR. HOLTZMAN: There were two different elements in what you said. One had to do with the

teasing apart of cognitive capacity versus other kinds of vulnerabilities which impair your autonomy.

PROFESSOR CHARO: Right.

MR. HOLTZMAN: The other was the second half of what you did, about how to split it apart and the kinds of studies. I agree with the second.

I am wondering if you really want to make that first distinction limiting this to cognitive capacity -- cognitive impairment -- because I took the essence of this analysis of vulnerabilities to be basically saying that what we care about is genuine informed consent. There are many ways in which it can come to be the case that a group of persons or a person who failed to be able to give genuine informed consent, only one of which is cognitive inability. Therefore, you need to ascertain whether -- what, if any, and which vulnerabilities are in play intrinsically in the study and then ask whether the right kinds of protections have been put in place to ensure that the consent can be informed.

I think that may be generalizable, Alta. I do not think you are going to want this watershed.

PROFESSOR CHARO: May I try to answer?

DR. SHAPIRO: Yes.

PROFESSOR CHARO: I think actually we could

split it differently. We could say research that is aimed at people's vulnerabilities, period, and do not distinguish. It has to go to the full IRB. And then another one that says research that involves people, who cannot consent for themselves because of incompetence, has this set of special rules about secondary decision makers because that is only about secondary decision makers. But I do not think that the issue of vulnerability is entirely about informed consent. I think it goes beyond that.

MR. HOLTZMAN: To what?

PROFESSOR CHARO: Well, for example, if I were doing research on a population that is made up entirely of African Americans, they are perfectly competent, perfectly capable of exercising informed consent, all right, but it may not be apparent to each person who is being recruited that this research is being aimed exclusively at the African American population. And because of the kinds of concerns we have identified before, about the way in which groups that have historically been discriminated against can be targeted for research that will further stigmatize that group. All right. I think it is appropriate for an IRB to ask the researcher why are you targeting African Americans in this research. Is there some reason for it?

It is not that any individual there is unable to exercise informed consent. It is that the structure of the protocol has a justice problem. See the vulnerability to me is not only about the ability to make individual decisions for yourself. It is about the justice of the selection of the subjects. Why are you picking these people and not others? How are you distributing risks across the population? And that is harder to pick up at an individualized level. And it has nothing to do with the individual vulnerability of those people. Right?

DR. CASSELL: Yes, it does.

DR. SHAPIRO: Alex and then Eric.

PROFESSOR CAPRON: I find myself in agreement with both of you.

(Laughter.)

PROFESSOR CAPRON: And it is not, I think, because I am of two minds but because I think you actually are not that far apart.

Your example, as you gave it, Alta, to me took on weight as an important example because you said the individual subjects would not be in a position, in being asked to participate, to know a very relevant fact, which is that they were not chosen solely as individuals but as African American individuals.

And because of the risks to the population, what makes this group vulnerable is being selected that way, the IRB ought to look at it and ought to ask that question.

The safeguards that they would put in place would be either redesign the study because you do not really need to look at African Americans or Jews or whatever other group. You could look more broadly and you will avoid the stigma aspect.

Do your research in a way that does not take -- does not lead to stigmatizing results. Go to some form of community consultation to say the results are important enough that even if they involve stigma, our group needs to know. I mean, they are about to do some drug now on -- a heart medication for African Americans, I read the other day in the newspaper because the existing treatments do not work as well as they should as they do with White people.

I do not know what the story here is but someone might say that is a good reason. We already know that this group has a disease now and we are looking for a specific treatment for the disease. In other words, they might have an argument.

There are any number of things depending on what the vulnerability is. The important thing is that

it got IRB review, full IRB review, not administrative IRB review and that the protections were put in. They do not have to have secondary proxy consent because the question of vulnerability is not mental capacity.

PROFESSOR CHARO: Right.

PROFESSOR CAPRON: So I do not -- I think we can do this all within a single recommendation and what we can pull out maybe for commentary is a description of which kinds of suitable safeguards are appropriate depending upon what you are responding to. This is another step towards making our recommendations aimed -- to indicate what objective we are aiming to rather than in the recommendation itself going into trying in subpart (a), subpart (b), subpart (c) to spell out if it is this, we do that. Just in the text we say examples of things because then we can be illustrative rather than trying to be definitive if we had covered all the bases. And I think that can be done in a single recommendation.

If I may throw one other form of vulnerability on the table, one of the main concerns is, are all patients who are recruited for research on their disease vulnerable for which a safeguard is having someone different than their own doctor do the recruiting, it would seem to me that that is an issue.

And could you add on any economic necessity on a patient -- in a patient who has some difficulty getting treatment, the opportunity to have free research to them is enormously attractive to me to the point where I may not exercise the kind of self-protection that someone without that particular vulnerability, economic and medical vulnerability, would exercise in making a judgment about the risks of the research.

And it seems to me again we ought to give that as an illustration and what remedies there are for that.

DR. SHAPIRO: Eric?

DR. CASSELL: Well, there may very well be justice issues in such a thing and they might have to be dealt with as justice issues but it is really a matter of informed consent. Alex said that people entering that study are not in a position to know that only X, Y, Z. Once they are not in the position to know, they are not fully informed.

DR. DUMAS: They are not what?

DR. CASSELL: Fully informed.

DR. DUMAS: That is right.

DR. CASSELL: They cannot make informed

consent.

DR. SHAPIRO: Rhetaugh?

DR. DUMAS: I am having a lot of difficult with the -- I am having a lot of trouble with the concept of vulnerability. It places the onus on the subjects for something that sounds to me like having to do with the way that the researcher goes about his or her business.

For example, if the person is not in the position to know some things about the research, then it seems to me that the problem is not the vulnerability of the subject. It has to do with the approach of the researcher. If they do not know certain things about the research, then they have not been fully informed.

The other thing that bothers me about this is the possibility of the danger that groups might be labeled vulnerable and, therefore, excluded from research that they really would need or could profit from being involved in. So I just struggle with that -- you know, with that concept.

DR. SHAPIRO: I think --

DR. DUMAS: I wish it had another word.

DR. SHAPIRO: Well --

DR. DUMAS: They are supposed to be informed

and no matter what their socioeconomic background is.

DR. SHAPIRO: Yes. Sure. No, I think we agree on that.

Bernie?

DR. LO: Well, vulnerability is sort of capacity. It depends on, not just the individual but the circumstances, and so to use the examples we have been throwing around, vulnerability does not depend on the sort of cognitive state of the individual or their ethnic background. It depends on what they are told, what steps are taken to mitigate the fact that, you know, you are getting care in the clinic that is also trying to recruit you.

And so, I mean, I think we need to say that more explicitly and to sort of make sure it does not seem to be a quality residing solely in individual subjects.

DR. DUMAS: Then I think we ought to use the -- we ought to talk about the situation and not about the subject.

DR. SHAPIRO: Arturo?

DR. LO: Vulnerable situation.

DR. DUMAS: Yes.

DR. BRITO: Between this proposed recommendation and I do not mean your version -- given

the older version of this proposed recommendation and the way we deal with the recommendation, I think, it is the next one, 3.12, with defining vulnerable -- or dealing with vulnerable populations and the analytical approach. The analytical approach to vulnerability deals with individuals but what -- this is really dealing with groups of individuals and talking about prospective participants. So I think this is where some of the complexity lies. It is almost contradictory when you are talking about groups in one end from the end of the components of the research and then you get into the part about how to define somebody who is vulnerable when you talk about individuals. And, I think, at least is where some of the confusion complexity lies.

So I think what we need to do is somehow make the transition from the groups to the individuals, starting with the components, and whether or not we define someone as minimal risk or not, but I could foresee some difficulty with, well, you are sitting on an IRB and they go, I do not know how to apply this because this may be a group of individuals that I do not consider to be vulnerable but we are placing this group at greater than minimal risk, but then you get to the individuals within that group, how do you define

when somebody is vulnerable within that group. There are some -- something here and just based on what -- something that Rhetaugh just said, it just makes it a little more complex.

DR. SHAPIRO: I think there are two things you have to always remember about these things so we do not make a hard problem even harder, that is what we are trying to figure out here is what level of review is required. We are not trying to say go ahead, do not go ahead, do it, do not do it, right. It is what level of review is required. That is all this is trying to deal with, not that it is dealt with appropriately.

DR. BRITO: Okay.

DR. SHAPIRO: We have to make some changes but that is all that is required and then --

DR. BRITO: When we deal with vulnerability --

DR. SHAPIRO: -- it is always true that if you want extra protection for vulnerabilities of any kind defined in any situation or any situational context, there is going to be an incentive not to go there for the research. I do not know how you get around that.

Even though we believe in justice and selection of participants and so on and we somehow have to learn or find a way and learn to deal with this issue or to live with it but I do not know that as long

as you say people are vulnerable, however defined, require extra protections or extra review or extra anything than you have a resulting, you know, extra hurdle to go over, which is -- I mean, it is fine as far as I am concerned but you cannot walk away from that issue. That is there.

DR. BRITO: Can I --

DR. SHAPIRO: Sure.

DR. BRITO: I agree with that. The confusion is that if somebody -- somebody that cannot give informed consent for whatever reason is by definition vulnerable.

DR. SHAPIRO: Right.

DR. BRITO: So when we get to the analytical approach to vulnerability we are dealing with individuals. Here we are giving recommendations on how to deal with --

DR. SHAPIRO: I understand that. I agree with that part of it. I agree.

Alta, and then who else? Bernie and Steve? Okay.

Alta, Bernie, Steve.

PROFESSOR CHARO: I think that there are -- in reaction to Rhetaugh's comments, I think that there really are different causes for people being in a

vulnerable situation. One set of causes has to do with an intrinsic characteristic and here I think very specifically about things that make people incompetent to make their own decisions and that includes age and mental capacity.

I think most of us would agree that somebody who is in a coma, for example, is going to be intrinsically vulnerable in any research setting.

I also think that as you said they raise very special issues about surrogate decision making and it is actually leading me to consider that we might want to drop any reference here to incompetent adults as well and clean this -- streamline this report even one more step and say that it applies to competent adults only because of the special issues that are raised when you have surrogate decision making.

We have got a report on capacity. We need a report on children. Fetuses and embryos are another very special case and that is why they are not being covered. And, therefore, when people cannot make the decision for themselves, it is handled elsewhere. This report is about people making decisions for themselves.

When they can make decisions for themselves, it is a situational phenomenon. Right? And so somebody who is in economic straits, somebody who is in

a patient-doctor relationship, can become vulnerable in a research context because of that relationship.

And then I think it actually is easier to implement Alex's suggestion about trying to come up with a way to express in lists the various ways we have observed over time perfectly competent people nonetheless becoming vulnerable in a research setting. Institutionalized persons who have lost the habit of acting autonomously, even though they have absolutely no mental impairment, but the institutional setting has a profound behavioral effect that renders them vulnerable in many research settings, da, da, da. And that might simplify this as well as destigmatize it.

DR. SHAPIRO: We have a lot of people who want to speak now. All right, Rhetaugh, then we will go to Bernie next.

DR. DUMAS: I would feel a lot more comfortable if we focused our commentary on the need for added protections because that is what I think we are talking about. And we would describe the situations where it is likely that added protections would be needed and that would take into consideration the groups, whatever we call it in vulnerability, but it would not label the subjects as vulnerable people but rather we would talk about the kind of conditions

that warrant special protections. Conditions like those that Alta just described where people are in the subordinate position to others and do not feel the freedom to say no and other examples.

DR. SHAPIRO: Bernie?

DR. LO: Somebody said that we need to keep in mind sort of the purpose of this discussion and it seems to me one purpose is as a filter. Sort of what level of IRB review or super IRB review do you need. And surely that is one of the ways we give added protection to say you cannot do this on administrative review.

But in addition to that sort of filtering, it seems to me you are also highlighting certain situations of certain populations in certain situations where you want to give the IRBs and investigators particular guidance. So it is not just a sort of setting up barriers. I think we also have to look at the other side and say now having called attention to the fact that if you are using patients in nursing homes or patients in the clinic where the -- all the investigators are also the doctors that not only have we called attention to this fact and said you cannot do this with administrative review.

But we also want to try and develop some

guidelines or criteria so that if you followed these certain criteria we are going to lay out, you can then say, okay, you can now go through IRB review by just saying we have done A, B, C, D and E, as the guidelines say, so we have addressed as best we can those factors that create the vulnerability and we have done it to the extent that standard practice is saying now it is okay to go ahead and do the research.

I would actually argue without going into a super sort of national and regional level of IRB review but I think we also want to hold out the idea that, by identifying situations, we can then focus attention on how you respond to or address or ameliorate the situation or the vulnerability.

There are a lot of standard things. You know, you wait until a patient recovers. You have some other person do the consent process, whatever. I mean, there are a number of things that if you do them all you may be able to say, okay, we recognize the vulnerability and we have dealt with it so now let's go on and do the research.

Harold's point about providing an incentive to sort of leave -- to sort of exclude people as subjects who are in need of having the research done, I think we should just flat out address it as we did in the HBM

report. We said, you know, we may appear to be creating an incentive to strip identifiers, all identifiers off all these samples just so you can, you know, push it through the system. Do not do that because it undermines the science.

I think we just have to say there are certain questions, if you are going to study certain questions, the questions really apply to people with vulnerabilities of the type Alta addressed. You know, people with dementia are the ones who need the dementia drug. People with severe depression need the depression drugs. You know, it does not make sense if you are interested in the question to try and doctor the protocol to leave out the people who are really the target audience for your research question.

We just have to say that and say that, you know, your scientific integrity has to play some role here that you do not do a study that has no significance scientifically just because you can get it through the IRBs.

DR. SHAPIRO: Let me just pose a slightly different situation, Bernie. I think I understand what you say. I was -- I understand the issue well if you are targeting people with dementia. That is what you want a drug for, people who are suffering from that

problem. What I was trying to think through in my head is what if you just take a simple thing, a pain killer or something, something which is -- and you are going to have to try this out in a population. And the question is in those kinds of studies where you just might have -- turn out to have a few vulnerable people just by the way you choose your sample, and the way the sample walks in the door, or whatever it happens, how do you deal with that situation because you want your results to apply to as broad a group of people as possible?

And it is that situation I was trying to think through in my head where the vulnerable people are not those you are targeting with a particular disease problem but they are just participating along with everybody else in a study.

DR. LO: Doesn't that depend tremendously on the nature of the research question?

DR. SHAPIRO: Sure.

DR. LO: I mean, I do not know a priori why there may be a reason to say that nursing home patients respond differently to pain killers than to people who are walking around in the community.

DR. SHAPIRO: Right.

DR. DUMAS: They are more vulnerable to begin

with.

DR. LO: Right, but I mean the real concerns I have are they are older, they have impaired renal function, maybe more of a risk for GI bleeding, all those things. But it seems to me those questions you can answer by taking a geriatric population in the community so to the extent you are able to address the pertinent questions --

DR. SHAPIRO: A good point.

DR. LO: -- now you start to get this genomics thing and say, well, in fact, there are biological differences the way different people metabolize drugs or respond to drugs.

PROFESSOR CAPRON: They have the nursing home gene.

DR. LO: Well, then you start to get problems with, for example, African Americans do not respond to hypertension medicines the way Caucasians do. So then you do have to --

DR. SHAPIRO: I understand.

DR. LO: -- if you are really serious about it, you have to target a particular -- but then there is a compelling scientific reason to do so. To go back to Rhetaugh's point, if in your consent process you say, you know, we are recruiting African Americans in

the study, the reason we are doing this is because the treatments we have developed -- that have been developed really do not work as well for African Americans as for Caucasians. All the studies have been done in Caucasians, we think it is important to do this.

So if you inform them, you take away the vulnerability, the people then have a choice as to whether -- you know, they say, "I accept that or that is a bunch of hooey and I am not going to do the study."

DR. SHAPIRO: Okay. Steve, you are on the list. I do not know if you still have concerns you are weighing. So is Eric and so is Larry.

MR. HOLTZMAN: Yes. I guess the one thing I would like to say is I am not as worried about being as PC as maybe I should be here on the concepts of vulnerability because at least the way I read this model, if one looks on page 58, it is trying to actually say that vulnerability is contextual or situationally bound. It could happen to anyone. Right? It just so happens the way in general the world is configured at the moment there are certain groups where there should be a presumption that they may be vulnerable in these ways.

So in that sense I take this as a guidance to IRBs to basically say, given the nature of the proposed design, are any of the following contextual vulnerabilities -- you should see if they are in play and that you should have a heightened awareness that the following kinds of populations are here, that they may or may not be in play and ask whether your protocols have addressed them appropriately.

I think that is the gist of what we said here, which again I think is a broader model where -- and then it is just now you can go through your algorithms and what do you do if they are in play or not.

DR. SHAPIRO: Eric?

DR. CASSELL: I think I have gotten lost. I look at this and I think, well, I am trying to think of research in sick people that does not deal with a vulnerable population. If they were not vulnerable, we would not be doing research on them. And part of the thing about the research on a population of sick people is then getting consent. Everything that might put them at risk should be -- they should be told about the things that are putting them at risk.

If they -- and that up to now we have said that handles the issue of their vulnerability. If there is a question of capacity that is a separate

issue and, in fact, that is dealt with here in another report.

But people are vulnerable. That is the -- I cannot see how separating them out as a special population is going to do anything but further complicate a situation which is already complicated. It does not make for greater protection. The protection in research risk should always be there. Everybody is potentially vulnerable and that is why we have risks spelled out in detail so that people know what they are saying when they can and that is why we also raise questions about the capacity of persons to give consent when something might, in fact, cloud their judgment.

DR. SHAPIRO: Larry?

DR. MIIKE: Well, we started -- the reason we went along this path is we had this crazy quilt of federal regulations saying this is a vulnerable population, this is a vulnerable population, this is a vulnerable population so we are going to an analytical approach. So let's remember that that is the reason. We were not addressing the whole issue about whether anybody in research is a vulnerable person. I think we all accept that and there are the other ways in which to deal with them.

Having said that, I still want to return to 3.11 and 3.12 because I think 3.11 and 3.12 are inappropriate in this discussion in this chapter because they are now, all of a sudden, taking out one particular type of vulnerability that affects your capacity to consent, which we have dealt with before in the capacity report. Granted it was limited to people with mental illness but it seems to me that if you look at this -- again I will say it -- it does not necessarily apply just to vulnerable populations. It applies to people with impaired capacity and one can talk about it in the text and say that we -- in one particular kind of vulnerability which affects the basic decision to consent or not, we have dealt there with a special situation and recommend that certain special procedures like a national body, et cetera.

But I do not think it rises to the level of a recommendation when we are talking in a generic term about the analytical approach to vulnerability.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: Now that we are actually looking at this chart and there is an opportunity to make comments about what is on it as well as what is not on it and how it is constructed --

DR. SHAPIRO: Do you want to give the page

number so everybody can follow?

PROFESSOR CHARO: Page 58, Chapter 3, Table 3.2.

I think returning to Alex's comment, and I think it is consistent with what I am hearing from the rest of the table, okay, what we would like to bring out is the idea that there are certain groups of people who, in certain situations, will be vulnerable and not in others. Patients could be considered vulnerable when it comes to being recruited by their doctor but not vulnerable when it comes to being recruited by a PI Ph.D. because the relational confusion is gone. Right?

A non-English speaking adult might be considered when being recruited in English but not vulnerable when being recruited in his or her native language.

And I think that is the goal of this table, although it is clearly not emerging well enough yet for everybody to receive the message that way without the problem of stigmatization of the group qua group. Right? And that is one problem.

The second is the very choice of what constitutes the groups on the list. I find the presence of pregnant women here to be infuriating

beyond description. There is no justification for it in my mind. If your concern is about patients during emergency situations and I have no idea where that differential came from but that is the one that truly annoyed me. And social, yes. Well, the only vulnerability they have is the fact that people view them as vulnerable, unduly differential and incompetent to make decisions for themselves. Whereas we happen to miss people who are institutionalized, people who are poor and people who are patients.

So to some extent there is a problem in ourselves in the sense of what groups are we identifying for an analysis that yields an understanding of what makes them vulnerable in which situations, the very choice of groups. And notice, by the way, that there is nothing here on race. The only vaguely ethnic thing is languages because we are scared to say it or because we do not know what to say but since the whole notion of vulnerability grew largely out of race-based and religion-based experimentation it seems like we cannot afford to not confront it.

And so I am finding myself --

MR. HOLTZMAN: You are not being fair.

PROFESSOR CHARO: -- less than fully satisfied.

MR. HOLTZMAN: The groups were selected because those are the groups specified in subparts B through D.

PROFESSOR CHARO: HIV positive injection drug users are not specified there. Children with low incomes and serious medical conditions are not specified there. I mean, so this goes beyond those groups. Right?

(Simultaneous discussion.)

DR. DUMAS: You said that there are some conditions under which a particular group may be vulnerable or may not be vulnerable. I think you are going after the wrong thing if we do that because the groups are the groups. I think we need to talk about the situations --

PROFESSOR CHARO: Right. So you want --

DR. DUMAS: -- people are inadequate at some moments or whatever and talk about the conditions.

PROFESSOR CHARO: So you want to talk about the situation so we would say situation one, physician recruitment. Physicians can recruit their own patients. Situation two, language. People should not recruit subjects in a language other than subject's own language. Right?

DR. DUMAS: It says that. When physicians

recruit their own -- no, there are conditions under which added protections are needed. One situation is where the sub -- the physician is recruiting their own subjects and the protections then can be described or in a situation where the subjects that are being recruited do not speak English. They need added protection. What other protections do they need?

PROFESSOR CHARO: Right. But you said let's focus on the situation and not on the groups so I am saying --

(Simultaneous discussion.)

PROFESSOR CHARO: -- focus on physician recruiters, focus on --

DR. SHAPIRO: Okay.

(Simultaneous discussion.)

DR. SHAPIRO: We got the point.

DR. CASSELL: A point of clarification.

DR. SHAPIRO: Yes.

DR. CASSELL: Just a simple English point. We are using the word -- this is what I meant. We are now using the word "vulnerable" in the same way we used to say "open to coercion." Is that correct?

DR. SHAPIRO: I think so, yes.

PROFESSOR CAPRON: Impaired autonomy. Their autonomy is impaired.

DR. CASSELL: So vulnerable in that sense, not vulnerable in a physical sense, the way we usually use the word "vulnerable." This is the old thing about prisoners -- excuse me. This is that same category that years ago was called that, is that correct?

DR. SHAPIRO: I think so.

DR. CASSELL: Okay. That is helpful to me. We might even put that in somewhere for people who have trouble with the word "vulnerable."

DR. SHAPIRO: There were a lot of hands up here a few minutes ago but this -- I think this issue is really central here and we are going to have to just take a step back and think this through and see what fits best here. I do not think we can get it all right now but those have been very helpful comments and we will have to work on that so I am going to suggest that we take --

PROFESSOR CAPRON: Is vulnerability to fatigue a category?

DR. SHAPIRO: Yes. For that reason we are going to take a break for 15 minutes now and then get together and continue other aspects of Chapter 3.

(Whereupon, at 3:04 p.m., a break was taken.)

DR. SHAPIRO: Colleagues, could we reconvene? Let me talk for a moment about how we will proceed.

We will -- Alta, I cannot compete with this conversation.

How we will proceed, first of all in a more global sense. We have a meeting scheduled in April. That is roughly a month from now. It is, in fact, however going to be very difficult to get all these changes made within that period of time and it does not give us much time to go back and forth as we want to ask the commission questions and get some feedback on it.

If it were possible to schedule a meeting early in May some time, and we will have to circulate amongst the members to see what is possible, that would in my mind be preferable because we would have a more productive meeting. And I do not want to go longer than that because then we run into logistical problems of getting this completed and done. So that is really a matter of a few weeks but that is critical given the work that has to be done on rewriting parts of this.

Now -- so we will circulate you later tomorrow or sometime very soon about whether it is possible to identify some early May dates. If that proves too difficult because of, you know, 15 schedules -- it is always difficult to find a date -- or 20 schedules, then we do our best to go to the April meeting and get

as far as we can in that context. Although that would be my second choice, it is certainly better than going any farther out.

So that our two choices will be -- we will not resolve it right this minute because we will have to check with everyone's schedule -- either to meet in the April dates we had been keeping, which I think as I said this morning were 18 and 19 or something like that -- 17 and 18, excuse me -- and whether we can find a day in early May, which I think is slightly preferable but it may turn out to be not feasible given everybody's commitments.

So we will go along that route and we will certainly be in touch on that issue.

With respect to the rest of the time we have this afternoon, I think I would like to go through the recommendations in Chapter 3.1 just so that one by one we can highlight what concerns people might have and to the extent that they have any so that we will know what issues we have to contend with and how we can deal with them.

So let's try to start. I guess Eric wanted to say something about 3.1 a long time ago but anyone, of course, the floor is open for everyone.

Trish, you have your hand high in the air.

PROFESSOR BACKLAR: I just wanted to say that I think that Alta's suggestion -- can you hear me?

DR. SHAPIRO: I can hear you, yes.

PROFESSOR BACKLAR: Okay. -- was a very good one and that we should think about that very seriously. I did not know that we had come to any agreement about it, that this report should look at competent participants.

DR. SHAPIRO: That is an issue I want to think through because I think while it has some very attractive components because it obviously simplifies a whole series of issues, I really want -- I want to think it through a little more carefully before going there.

PROFESSOR BACKLAR: But could we have a chance to discuss it?

DR. SHAPIRO: Oh, yes.

PROFESSOR BACKLAR: Before we leave tomorrow.

DR. SHAPIRO: Absolutely.

PROFESSOR BACKLAR: Okay.

DR. SHAPIRO: Absolutely. If we do not get to it this afternoon, we will put it first in the agenda tomorrow.

Okay. Let's now talk about -- if anybody wants to raise any issues just going through these one

by one. Eric?

DR. CASSELL: This is 3.1?

DR. SHAPIRO: 3.1, yes.

DR. CASSELL: Not 3 -- okay. I am sorry.

DR. SHAPIRO: Okay.

(Simultaneous discussion.)

DR. SHAPIRO: Eric does not want anything right now.

Alta?

PROFESSOR CHARO: On 3.1, two things that occurred to me looking at it. The first is probably the easier one which is that it contains two different ideas that might be better broken out. The first is in the first sentence about uniform -- consistent analysis of risks and harms of benefits and the second has to do with a component analysis, which people may choose yes or no to adopt as the consistent analysis they are going to apply.

DR. SHAPIRO: Yes.

PROFESSOR CHARO: With regard to that first sentence on the analysis of risks and harms should be consistent, I would prefer if it specifically said and should include nonphysical harms and benefits.

I had a discussion at lunch about the possibility, and this would be one place one could do

that, of an explicit acknowledgement that nonphysical -- or that noninvasive research we expect will generally not pose significant risks of harm, although IRBs would certainly be looking for the circumstances where it does because of sensitive issues, sensitive populations, whatever.

But that in this way we can strongly signal that there is a deep hope that while we are going to be looking at both physical and nonphysical harms and benefits and physical and nonphysical kinds of interventions in research, that we also expect categorically that you may be able to move through certain areas of noninvasive research rather rapidly.

DR. SHAPIRO: Eric?

DR. CASSELL: I found my place again.

I would like to hear some more discussion of the advantage of breaking research into components because I can think of disadvantages. Either the research is what it is or it is not, and breaking it into components would have to be justified, I think.

DR. SHAPIRO: Okay. I think -- I do not know who wants to answer that. Eric, do you want to answer that or do you want me to answer it?

DR. MESLIN: I think you can.

DR. SHAPIRO: Okay. The notion was that we

are trying to distinguish between research that offers some potential benefit directly to the individual involved and research that is not. And if you classify every -- it is sometimes, I think, a little misleading to classify the whole project as offering a potential benefit when, in fact, only one small component of it does and you might have quite risky components that are only research oriented and that you do not want to really think of this as just offering -- the entire protocol offering a direct benefit just because some small section of it does.

So I did not want to drag -- to use the now disgraced term "therapeutic/nontherapeutic research." I did not want to create -- speaking for myself -- the whole thing is therapeutic just because some small portion had some potential benefit.

DR. CASSELL: Well, I am trying to think of some research that is directed towards the therapy in which the benefit is not in one small component of the therapy while the risks are in many of the interventions to find out whether that therapy has been useful. In which case -- but the thing is a package. You could not do the one without the other.

Now if you had -- if you could say where one part could be done without the other, that is a

different issue but then we wonder why --

DR. SHAPIRO: That is a different issue, I agree.

DR. CASSELL: -- put together in the first place.

DR. SHAPIRO: Agreed.

Alta?

PROFESSOR CHARO: Well, of course, there is always a risk your example is not the right one but here is one that occurs to me. You are -- I am going to take a biomedical example. You are testing two different drugs for the treatment of mild depression. Right? So perfectly competent people and the research does offer the prospect of some personal benefit because you are testing two drugs, right, against one another.

Alongside this the PI proposes to do a variety of biopsies -- not biopsies here but let's say bone marrow samples, tissue samples.

MR. HOLTZMAN: CSF.

PROFESSOR CHARO: Say what?

MR. HOLTZMAN: CSF.

PROFESSOR CHARO: CSF. In order to create a database that will be of some use in the future. It has not got any use now for this particular protocol.

It is not about evaluating the drugs and the outcome but you are going to be trying to collect information for the future.

Wouldn't you want to look at that part of it separately and ask are the risks reasonable for that part of it?

DR. CASSELL: Well, my experience is receding into the past but my more active colleagues might point out that is just bad research. That is simply bad research. They are doing two different things under the guise of one study and if they are out to get a database about the spinal fluid and they are out to hook that to a therapeutic thing, I think a lot of IRBs would have trouble with that one out --breaking up into components. Why are they doing that in the first place? The research as a whole does not stand together.

If, on the other hand, they say we need spinal fluid to find out what happens to this or that agent in the spinal fluid and as long as we are there, instead of just taking 10, let's take 15 ml of spinal fluid, once again we would say but that is not part of your research even though, in fact, the risk is taking place in another part of it.

So I think as a whole you are criticizing the

whole piece of research. I do not see the point of breaking that into two.

DR. SHAPIRO: Other comments or questions about this?

PROFESSOR CHARO: Eric, I will be happy to yield that that example was a poor example but I know this has come up repeatedly in my own IRB. I know that there are examples out there. I would not want to abandon this until we could actually come up with some concrete examples as Bernie often points out.

DR. CASSELL: Well, I would like to hear the concrete examples. I mean, this -- put them on e-mail and let's see the concrete examples and see how they hang together and if they are persuasive I am easy. I am so compliant.

DR. SHAPIRO: All right.

Steve?

MR. HOLTZMAN: Well, here is a real example of a protocol, and again you could argue it is actually two different pieces of research put together, and it is becoming very standard where if you are doing a drug trial you will also want to collect a DNA sample such that you are able then hopefully to correlate a polymorphism with drug response.

Okay. So it is not going to be helpful --

that piece of research, the correlation -- the pharmacogenomic marker research is not going to be beneficial to that patient, right, but the only way you can do that research is in conjunction with your drug trial because those are the only subjects.

Now again you could say there are two different pieces of research going on.

DR. CASSELL: No, I say that is one piece of research that part of which is beneficial -- directly beneficial to the patient but the important part of the research is why are those patients responding to the drug and that is what your genetic analysis, I take it, is meant to answer.

MR. HOLTZMAN: Right.

DR. CASSELL: It is not a separate piece of research.

MR. HOLTZMAN: No, but again I am not sure why you say it is -- which is more important. We are trying to get that drug registered. We are doing a Phase II trial and we are collecting and I think what this is saying is with respect to the drug trial, it is a cancer drug, right, what we ought to be doing is making an adjudication on a different standard than with respect to the collection of that genetic sample.

Now in that case we would probably say that second piece of the protocol is minimal risk, all right, and, therefore, it works. Okay. And that is the -- then the component analysis works in that case. You are looking for a case where -- and we had one in the text, didn't we, where judged as a whole it would be yes, whereas judged component it was no. And maybe we ought to review that case and see whether that elucidates matters for you.

DR. SHAPIRO: I agree it is a question of being convinced. I agree with the -- so we have to provide a persuasive example. I agree.

Other comments with respect to 3.1?

DR. LO: 3.1?

DR. SHAPIRO: 3.1.

Again if you have particular language changes those ought to just be handed directly to Marjorie.

Alex?

PROFESSOR CAPRON: I apologize. You will tell me quickly if I am addressing something that has been resolved but the whole division in the last few sentences between the components designed solely to answer one and components designed to answer the research questions struck me as an odd division. Have you just resolved that?

Because what it suggested was that if you are trying to answer the research question and offering the prospect of direct benefit to participants, you could only permit that when you judge the risks and benefits as reasonable in relationship to those associated with accepted practice.

Why the benefits to society fall out there is just not clear to me? In other words, if you have an intervention which you would allow because of its benefits to society, even though it -- the risk and benefits are not reasonable in relationship to those of accepted practice because the benefits to society are so great, why do you forget about those benefits to society if you are now offering a prospect of direct benefit to participants? It ought to be easier to approve. Does that make sense?

I could not -- and conversely in the previous sentence when it says components designed solely to answer the research question and offer no prospect of direct benefit should be permitted when the IRB judges the risks are reasonable in relationship to the potential benefits to society but is there no limit if you look at it the other way. Is there no limit on the relationship between the risks and the risks that people would ordinarily run in interactions with

researchers? That is to say could a very great benefit to society be enough to allow a research project which would impose extraordinary risks?

I mean, the example I always think of is there were a lot of people apparently in the astronaut corps ready to go to the moon when all we had was a way to get up there and no way to get back. And the argument was the benefit of society, which was partly scientific and partly patriotic of being the first to get to the moon was thought by those people to be fine and NASA said, "No, we cannot do that." And that was partly prudential that the reaction against it will be terrible but it was partly also ethical. It would not be right to take advantage of people's willingness to do something to send them on a suicide mission just so that we can be first on the moon.

And so there is some limit even when there are great benefits to society -- potential benefits to society. There is some limit to what researchers and IRBs ought to approve. So that it seemed to me the bifurcation of those two -- it was odd to have one element only counted in one place and one element counted on the other place. So that is -- that has not been discussed yet. Okay. I hope you can address that.

DR. SHAPIRO: Yes.

Steve?

PROFESSOR CAPRON: Uh-oh, I am worried.

MR. HOLTZMAN: Well, you say it is odd but I think that is the intent. So let's take what you just said. Components designed to answer the research question offering the prospect of direct benefit should be permitted. That one. And you said, well, when would it be the case, Alex, that if the research -- the risks were unreasonable in relation to accepted practice that a general benefit to society nevertheless lets you go ahead? What would be an example of that?

PROFESSOR CHARO: I have got one.

MR. HOLTZMAN: Please.

DR. SHAPIRO: Go ahead.

PROFESSOR CHARO: Pain killers for mild conditions.

MR. HOLTZMAN: Then it is not unreasonable in relation to accepted practice. That is a classic example.

PROFESSOR CHARO: Why? If you have got perfectly good pain killers on the market --

MR. HOLTZMAN: It is not unreasonable because the harm is essentially zippo. It is transitory.

PROFESSOR CHARO: You are the guy with the

broken ankle. Are you telling me that pain for six weeks is not a harm?

MR. HOLTZMAN: It is not unreasonable. I mean, this -- no, come on. The risks are --

PROFESSOR CHARO: Right.

MR. HOLTZMAN: -- risks and benefits are reasonable.

PROFESSOR CHARO: It may be that again it is a matter of how clear these things have to be. If you are talking about two cancer treatments that are standard and known to work and somebody wants to introduce a third that they are testing without, you know -- without -- how to put this? You know, placebo versus experimental and you are never going to give them the standard arm and the risk is now death. We understand that that is -- but this is aiming at preventing, right, that is why it is keyed to standard practice.

MR. HOLTZMAN: Right.

PROFESSOR CHARO: But --

PROFESSOR CAPRON: Steve, let me come at your question in a slightly -- or get to an example.

MR. HOLTZMAN: Start with an example.

PROFESSOR CAPRON: What I am saying is in the previous sentence we have apparently allowed research

with no prospect of benefit to go ahead when it is of benefit to society and we have not placed any apparent limit on that. We have said simply if -- when the risks are reasonable in relationship to the potential benefits of society. So, yes, there is --

MR. HOLTZMAN: Right, there is a limit.

PROFESSOR CAPRON: There is some risk but the benefit to society outweighs that. Now we add -- we say, oh, it turns out we can actually benefit the subject. And according to this sentence that prospect of the benefit to society drops out of the calculations and now we only ask is this proportionate. And let me give you an example.

Somebody has a bad form of cancer. There are not -- there is no cure now but there -- people with this kind of cancer generally get palliation. The accepted practice is palliative treatment. If they go through this experimental thing there is some prospect that it might cure them but it is very, very small. There is certainly prospect that enough will be learned that, five years from now we will do much better with this kind of cancer than we do now, which will be a benefit to society. But the person is going to accept a much bigger risk if they go into it than if they get accepted treatment, which is just palliative

care.

I would say that would be a circumstance in which we would say a person could agree to do that.

MR. HOLTZMAN: But I think --

PROFESSOR CAPRON: And it is a --

MR. HOLTZMAN: I do not think so because I think it is the way you just juggled the example. All right. Because if it is merely palliative is the current practice and what you are going to do is only live for three months, then the risk -- and you built it into the risk/benefit. If, in fact, you gave me the example where the palliative therapy, all right, was going to give you a two year life expectancy and that there was this new drug, all right, very, very, very low probability of success at a cure, all right, you are going to die if it does not in a month --

PROFESSOR CAPRON: Right.

MR. HOLTZMAN: All right. -- but you are going to have an enormous knowledge that you learn for society, you would not let it happen. So I think you have built it in -- I think the way you --

DR. CASSELL: That was --

MR. HOLTZMAN: What?

DR. CASSELL: That was the childhood leukemia --

PROFESSOR CAPRON: Exactly. That is bone marrow --

DR. CASSELL: If they died without treatment it took them longer to die. With treatment, they bled to death. Without treatment, they died of infection and it took them longer to die.

PROFESSOR CAPRON: Yes. That is the story of bone marrow, isn't it? Chemotherapy, yes.

MR. HOLTZMAN: But I think that is being built into the risk reasonableness.

PROFESSOR CAPRON: And I think the only reason -- the only reason that was permitted was the sense we are going to make progress on childhood leukemia with this and it is obviously complicated because the kids were not the primary consenters but together -- well, you know, it is --

MR. HOLTZMAN: No, but actually -- but, Alex --

PROFESSOR CAPRON: But if you take -- but I am saying if you take that element out of the story and say that it was adult leukemia that went through the same process so you did have -- you would certainly say those people could make that choice. All I am saying is it is odd since we apparently would allow it to go forward with no benefit to the person only weighing the

benefit to society. Why once we add in benefit to the person does benefit to society drop out of the good side of the scale? It does not make any sense.

MR. HOLTZMAN: The question is whether you let it influence the tipping of the scales. Obviously if it has that, too, it is better. The question is whether that can tip the scale. So no one denies that it would be nice to have that as well. Will you let that tip the scale? That is the question. I read the sentence as saying leaving it out because it is not allowed to tip the scale.

PROFESSOR CAPRON: Well, I read it saying it is not on either of the pans of the scale at all and it just seems to me odd. I mean, if I were doing research that involves some risk to people, I would say, oh, I do not intend to benefit them at all because then all I have to do is convince you that it is beneficial to society and then you make a judgment. Once I admit there is a benefit to society, as I read this sentence, boom, benefit to society -- benefit to the individual, benefit to the society disappears and I have to win it on benefit to the individual, which may be minuscule. I mean that may be a one in a 1,000 chance this person is going to benefit but I have not lost the benefit to society that was there before I claimed the benefit --

DR. CASSELL: Just a quick --

DR. SHAPIRO: Yes, Eric?

DR. CASSELL: The way it is set up like components, I can see a situation where the therapeutic component gets dropped out, you cannot do that. It is too risky but all other research components are fine, you can do them all. So the component that has nothing to do with producing anything in the long run but is absolutely no risk gets to go ahead but the therapeutic part of it that has real risk gets stopped. I mean, they are either one piece of research or they are not.

DR. SHAPIRO: Well, putting -- holding on that particular issue and just looking at the sentences here, I agree that the first of these sentences, which only balances risks to the individual against benefits to society without limit is troublesome. I mean, I think that is my own reaction to that. That is troublesome and needs to be rethought in some way.

Now the second sentence is something which I think is -- now that I have thought through but that is a question whether on the second component wants to -- we want anything further in there? We get to what Alex was saying, is at least you should be able to put in the scales something about the potential benefits to

society.

Now in this -- when we went through this before what we were always worried about was that people would pump up this potential benefit to society and overwhelm all other considerations. You know, you can claim it is just a claim and a big enough claim seems to just put all other things --

PROFESSOR CAPRON: And a lot of research does not pan out.

DR. SHAPIRO: Yes. And so that was at least my recollection of the motivation here and I am not yet fully comfortable with just what the right way of dealing with that problem is.

Alta?

PROFESSOR CHARO: Well, I am finding myself wondering if it is not exactly about components that offer the prospect of a benefit. It is components that involve testing interventions for which there are alternative interventions that are currently out there. Alex's example of there is nothing else out there and this intervention offers some small possibility of benefit and isn't it silly for us to not also consider the societal benefit, I think that part of what makes that example compelling is that there really is no alternative that is being foregone.

And I think that what people had in mind here but perhaps did not express exactly that way is, the situation where you are asking people to forego an existing option with relatively well understood advantages and disadvantages, and instead to opt for the experimental research intervention.

And the question is should that offer be permitted on the basis that the research interventions, risks as compared to the standard options, are reasonable in relation to the benefit society will gain from having tested it or rather do we have to ask initially is there some reasonable relationship between the risks of the research intervention and the risks or disadvantages, whatever, of the standard options?

I think that this was trying to get at that time and that is a slightly different way of phrasing it and I think it is a somewhat narrower range of things. And it is similar to your question about the pure research intervention and the astronauts in the sense that we do have an instinct that it is appropriate no matter how parentalistic it is to say that there is some kind of absolute limit to the amount of risk we will allow people to take on even after having been -- even after having given informed consent if there are standard options available to them

regardless of the societal benefit.

I agree with you instinctively that we do not need to eliminate societal benefit from this but I have been present at many discussions where it has threatened to swamp the discussion which should have started with is this a reasonable increment of risk over the standard options in light of the reasons why the standard options are not the perfect choice for this patient first and then also in light of what might be learned for the rest of society. That last thing tends to swamp the discussions.

DR. SHAPIRO: Well, maybe some approach -- I have two things to -- we have two things to work out here and I do not think we can work them all out here this afternoon but one is what we identified as problem with the first of these statements that Alex identified, and I think that is a problem because it has no limit whatsoever. The second is an issue that I guess the way Alta just phrased it was, you know, should you first try and resolve in your mind whether it is reasonable and come to some kind of conclusion on that.

And then say, well, are these other societal benefits worth deviating from that and I guess it is the kind of operational thing you want to consider.

And the problem we have is to prevent the latter from always overwhelming any of the former and I think that -- I do not know just yet how to resolve that problem.

Now the question we will have to ask ourselves is if we make the suggested change in the first of these, that is get some limit in there, and also make the change of some kind and, second, what does that do to the concept of components and I have not thought that through yet.

Bernie?

DR. LO: This is a very interesting discussion because we are now going back to saying what are the problems, what are the issues that we are trying to address. It sounds like we have identified probably two different but related issues. One is this notion that the alleged benefits to society may overwhelm any risk to the individual using conventional analysis.

The second is, I think, Alta's example of studies that have as the control a standard therapy that works fairly well and saying we are going to try something that we think may work better but may be worse, how can we justify even asking you to consider going off standard therapy. That is sort of the radical mastectomy versus lumpectomy plus radiation

study.

So you want to be able to do those studies because, in fact, the fact that standard may not be that it is reasonable. But justifying that is sort of trickier than Alex's example and you do not have a lot to lose because your prognosis is --

PROFESSOR CAPRON: But the justification if it exists is benefit to society, isn't it?

PROFESSOR CHARO: Not --

DR. LO: I think your --

PROFESSOR CAPRON: But you will know -- even if it fails --

DR. LO: Right, you will --

PROFESSOR CAPRON: -- you will learn something. I mean, take the current Parkinson's fetal cell transplant thing. It failed, that is to say it did not help and it seems to have hurt some of the people but you learned a lot in that process. And ergo the fact that there was -- if you were only looking at it on the individual basis you would sort of say -- well, you would always just stick with the standard. Just do whatever the best clinical judgment says is right for this person. All of research in the end says benefit to society.

DR. LO: I agree with your point that it does

not make sense to throw out the benefit to society.

PROFESSOR CAPRON: Yes.

DR. LO: But I guess I am concerned now that we had an answer in terms of our component analysis but I do not think we were clear on what the problem was and now you are saying these are the problems, is our component analysis that we so carefully laid out the solution?

Because I think when I think of examples that have come up, and you can think of bone marrow transplant in people with metastatic breast cancer and things like that, the way it has been dealt with is not to sort of analyze the risks and benefits differently, it is to say let's really make sure you are choosing people who do not have -- who have as little to lose as possible because they are not doing -- they are unlikely to do well with standard therapy. Let's really make sure that the consent process is robust, X, Y, Z. So it is not so much weighing the components. It is putting in added protection.

So I guess I am a little concerned and you have sort of taken a sort of conceptual innovation that seems nifty but may not fit the problems with it right now.

DR. SHAPIRO: That is correct.

Alta?

PROFESSOR CHARO: Two things. First, with regard to your radical mastectomy/lumpectomy/radiation example, I think the justification for that when done in my opinion most appropriately did not start with value to society. It started with the fact that radical mastectomy posed a problem for some women. They were very unhappy at the price they had to pay for longevity and were very interested in looking at alternatives.

And that had to be the starting point and in all of these areas of research ideally what you do is you start with populations that have some reason to find the standard option particularly unsatisfactory. And work with them first because that is where you are talking about a risk/benefit balance with the new intervention that is most favorable at the individual level, and that has to be important to this.

If you start with a societal analysis it takes away the incentive to some extent to distinguish within potential recruits those for whom there is a particularly good reason to try out the research intervention and those for whom there is very little reason for it.

Wait, wait, wait, let me just -- before I

forget, let me just mention that -- oh, God, it is slipping away. Oh, the component analysis. Let me just throw out one more example for us to think about as we go through this.

The Beaver Dam Wisconsin Eye Study. It is one of these longstanding studies where they have had a population they have been working with for over a decade, longer, 20 years maybe, and they keep going back over and over the same population to keep studying things because they have got this nice collection of information and there were parts of that study that involved giving people eye exams and giving people various kinds of interventions but they repeatedly go back to that population now to just do perfectly nontherapeutic research. Just data gathering of one sort or another.

And a question that arises is whether or not these should be viewed separately or they should be viewed as part of the overall risk/benefit balance of all of the levels of participation. So it is an area in which we have certainly decided to take it component by component and each component has been evaluated on its own.

DR. CASSELL: Can I set the record straight?

DR. SHAPIRO: Yes.

DR. CASSELL: Lumpectomy started with Criel in the Cleveland Clinic in the '50s before there were persons in medicine -- I mean, when people were just patients and also a British surgeon, no radiation at that time, so it was already on the table as a therapeutic option when the NIH picked it up.

DR. SHAPIRO: Somebody here had -- Alex?

PROFESSOR CAPRON: I was going to also comment on the design of those studies but I think I agree with Eric's point. I think that the component analysis, which in a way is not unique to us -- I mean, this is the point Bob Levine has been bearing down on for a long time -- is helpful and I do not think we have to abandon it simply because we have gotten to a point in saying we have to be careful that you find a means of expressing the balancing that is going to have to go on. And I agree with Steve that -- you know, I think there is tipping and there is -- and there is improper tipping or overweighting with something.

We are not going to -- this is not a regulation that is going to solve that. I think we simply have to say that it is important to separate them.

As to the first, the prospect of benefit to society can weigh but there is some outer limit. As to

the second, when you are focusing on benefit to the individual, the natural reference point is what they would face if they were not doing this, what the benefits and risks of accepted treatment are, but the benefit to society can also count here as a reason for allowing that component. I mean, it -- and I think that -- I was not asking for anything very radical. I just thought both of those aspects should be reflected somewhere in this language.

DR. SHAPIRO: And I agree with that. Marjorie?

DR. SPEERS: I have a very simplistic view of this model and how this model works. Maybe I am wrong and I know you will tell me if I am.

(Laughter.)

PROFESSOR CAPRON: Keep it a secret then.

DR. SPEERS: We have a study and that study, the whole of the study, the whole study in a sense is designed to yield knowledge that should be of benefit to society. Now in that study we are going to break it down into two kinds of components. And so if we take a drug study or to just generically say we have a drug study, we are going to give a drug and we are going to have some way of measuring the outcome of that drug.

Now the drug component and that outcome

measure component are the two components that make up that study. As we say here, both of those components are designed to answer the research question in a sense. I mean, that is why we are giving -- they are intimately tied together, which means if one -- this goes back to Eric's point.

If one component does not pass the ethical test to be in it, you do not proceed with the other because they are tied. You cannot give the drug if the outcome measure is not acceptable. You would not measure the outcome if you could not give the drug so they are intimately tied together.

What this model says is that the way that you evaluate those two components is that the outcome measure is measured in terms of any risks that associated with that outcome measure, a blood test, a scan, a biopsy or whatever, a psychological test, whatever, and that is evaluated in relation to the potential knowledge to society. Knowledge that will gain the potential benefit to society.

The drug on the other hand in and of itself should be evaluated against accepted practice. The drug -- the risks and potential benefits of that drug should be evaluated according to what are the risks and potential benefits of accepted practice.

PROFESSOR CAPRON: But, in fact --

DR. SPEERS: And it is the tying -- but it is the tying of those two together --

PROFESSOR CAPRON: But suppose that the outcome measures you are doing involve no risks. You know, you are taking urine samples or something and that is all the outcome measure you have. It does not involve any risk collecting urine samples.

So you would say, well, obviously that makes it but the drug itself is -- as in the example I gave -- is a good deal riskier than the current treatment, which is palliative. It would fail on that ground and yet -- so it -- when you look at the component that involves "the benefit", which is the drug, which if it would work -- a one in 1,000 chance it will work it will help the people so it falls in that second category. You would have to reject it.

It does -- I mean, in other words, the component analysis says that when you are giving a benefit all you care about is the benefit to the individual. Whereas, you are giving the drug independent of the urinalysis, you are giving the drug to see if it makes a difference.

I mean, suppose the drug were penicillin. You do not have to do any analysis. The person stops

having pneumonia. I mean, before penicillin, you come up with penicillin, you give it to someone, the outcome analysis is that they live instead of dying of pneumonia, and so you would not have a second component. The only component you would have would be the one that is potentially beneficial and it turned out to be dramatically beneficial. And yet it should be evaluated in part because if it does work it will have benefit not just for this individual but for society.

DR. CASSELL: And, Marjorie, your own example said the drug has benefit. Well, how do you know it has benefit if you do not have an outcome measure? And if the outcome measure is in a different component I do not quite understand how you separate those two -- incidentally, penicillin has never been studied in that setting. It never was studied.

PROFESSOR CAPRON: Never studied.

DR. CASSELL: Never studied. It was --

(Simultaneous discussion.)

PROFESSOR CAPRON: Yes, right, that is what I meant. It was just -- it was given and the effects were so dramatic that --

MR. HOLTZMAN: Maybe -- I think by choosing the outcome measure where it was intrinsically tied to

the drug, I do not think that is a good example, Marjorie, so let me try one.

We have a new anticancer drug. It is of an absolute new class. It is an inhibitor of the proteozome pathway. One of the things we are looking for as a society is drugs that attack totally new pathways. This is a real live case. Okay.

So we want to go into -- as is typical in cancer Phase I's, we are actually dealing with cancer patients. We are designing the studies that in addition to looking to whether the people will respond to the drug, which you are just going to do by imaging and seeing whether you see tumor shrinkage, you could imagine you would also like to be going back in and taking repeated biopsies or whatever to then do studies about whether you can correlate shrinkage with changes in transcriptional profiles of different genes so that you could develop a marker.

Okay. The way this works -- if you take the drug study, all right, because we focus on the alternative to the individual, we do not go into patients who are drug naive, who have never seen an anticancer drug. We have to go to patients who are refractory to the common practices. It does not matter how much there may be a benefit in getting a new class

of cancer drugs to society, we are -- it is only ethical for us to go to the refractory patients. And the component analysis says focus on that point. Again we could come back to how we elaborated on it.

With respect to those additional studies that I want to do to look for changes in transcriptions of genes, okay, this would say you have got to look at that separately and probably the conclusion is if you did imaging, noninvasive imaging, that is cool. All right. But if you are actually going to be invasively taking samples --

DR. COX: Biopsy.

MR. HOLTZMAN: Biopsies, which is not intrinsic to measuring whether you are getting the drug outcome, all right, then you have got to measure it against the overall benefit to society versus the risk and if I imagine that -- I was talking now brain tumors, and I am going back in, I probably ain't going to get there because of the risks. So I think that is a better example.

Now the question is we could take that example and ask why would we -- how would we analyze it differently with a noncomponent analysis and also what you were suggesting, Alex, to the changes of the ways that he is thinking, how does it work with it?

PROFESSOR CAPRON: May I modify your example just in this one way? Suppose you had a --

MR. HOLTZMAN: It is a real example. Modify it.

PROFESSOR CAPRON: Yes. Suppose it a very strong case that the drug that you were developing, this new pathway drug, will work less well where patients have already been beaten up by other drugs. I mean, just for whatever reason. So that you wanted to be able to go with patients who were more naive. Or put it this way: That you would learn much faster. The others may respond but it is -- you have got a complication overlay. You are talking about a five year program with 200 patients. Whereas your naive patients you believe you could do it in a one year program with 20 patients.

MR. HOLTZMAN: You cannot do it.

PROFESSOR CAPRON: Now there would be -- when you say you cannot do it --

MR. HOLTZMAN: I cannot do it in the U.S.

PROFESSOR CAPRON: Well, but --

(Laughter.)

PROFESSOR CAPRON: What I would ask would be if there were an argument that the -- you have modeled this so well that actually we firmly believe that to be

the case, that we could either expose 20 patients and know in a year if this works, and if it does work we have a treatment which will be of benefit to everybody, including the other 180 that would have been in the study and many more. If it does not work we also know we should drop this line of research and go back to the drawing boards and whatever.

MR. HOLTZMAN: Cannot do it.

PROFESSOR CAPRON: Who says you cannot do it? The FDA?

MR. HOLTZMAN: Pretty much.

PROFESSOR CAPRON: Any IRB in the country?

MR. HOLTZMAN: Basically the whole history of research and the ethics in the U.S. of which you have been a major part.

(Laughter.)

PROFESSOR CAPRON: The whole question of treating cancer research -- I mean, you are saying this as though it is written somewhere and I want to know where it is written that you cannot do it. But I --

DR. CASSELL: We have no evidence that it is going to work. That is why.

MR. HOLTZMAN: Again, it takes -- you know, Alex, if you go to the point at which we have done incredible computer modeling, and I say it is going to

work, it is a different gig.

PROFESSOR CAPRON: No, what I am saying is that there is every reason to believe from the studies that you have done that getting usable results out of patients who have gone through other chemotherapeutic agents will be much, much harder, that the data will be dirtier.

MR. HOLTZMAN: That is right. So --

PROFESSOR CAPRON: And, therefore, you are going to expose a lot more people to get a satisfactory --

MR. HOLTZMAN: Right.

PROFESSOR CAPRON: -- and with enough power in your statistical --

MR. HOLTZMAN: So but here are these people, these real live people, these 10 people who have cancer.

PROFESSOR CAPRON: Right.

MR. HOLTZMAN: All right. Standard regimen says give them taxol. All right.

PROFESSOR CAPRON: If it does not work, give them X.

MR. HOLTZMAN: Right. Three of those people will respond to taxol. All right. You are saying those are going to forego taxol for this potential

benefit for society. That is --

PROFESSOR CAPRON: That is the issue.

MR. HOLTZMAN: That is the issue.

PROFESSOR CAPRON: Could they consent to do that?

MR. HOLTZMAN: Right now I do not know whether they could consent to do that. Okay. But we would not be approved certainly by the FDA and the NIH would not.

DR. CASSELL: You would not approve it either. You are asking people to forego effective treatment on the chance that these guys and their mice have done so well, but do not take the effective treatment for --

MR. HOLTZMAN: No, it was even worse. It was on the -- maybe they work in the mice but it was because you could more rapidly learn whether that which worked in the mice actually works in humans.

PROFESSOR CAPRON: No, I was saying that when you -- you took the group of mice or whatever and gave them taxol first and then tried your other thing --

MR. HOLTZMAN: I understand.

PROFESSOR CAPRON: -- you could not get --

MR. HOLTZMAN: I understand what you are saying.

PROFESSOR CAPRON: If the results are that it only -- if the existing treatment now only works in

five percent instead of 30 percent of patients and 95 percent are not helped -- I mean, at some point it seems to me -- I agree with you.

MR. HOLTZMAN: Alex, you and I have actually had this discussion. We have another drug which we believe would be very effective in MS, all right, revolutionizing the treatment of MS, which we believe will work much better in interferon naive patients. Interferon is standard of care for MS patients even though it does not work in everyone. In the U.S. we have to do it in people who are refractory or relapsing off of interferon. When you say why? That is the interpretation. Unlike I have got a new pain killer example, right, where all I am asking people to do is have a little bit of headache an extra two hours.

PROFESSOR CAPRON: What if they turn out to be refractory to your experimental treatment? Can you then put them on interferon? I mean, MS is not going to be instantly lethal for people.

MR. HOLTZMAN: It has to do with what is going to be the potential effects. You are asking the question is it --

PROFESSOR CAPRON: No, we are not sitting as an IRB.

DR. SHAPIRO: There is a -- I want to turn to

Bernie in a second but there is an issue of whether an established treatment exists and if it -- whatever that treatment is -- cures a small enough proportion, it is like zero, and so if you get close to that what you are talking about is whether there is a reasonable existing therapy or not. I think that was the difference in the two examples you have.

But anyhow, Bernie?

DR. LO: I guess I am trying to sort of get a sense of where we stand now. We have had a very interesting discussion for a while on something we have worked on for a long time. I am just concerned that when this gets issued -- if this gets issued in this format, if we cannot understand it and do not quite see what it is all about, I think the people who read it are going to have trouble. I am just trying to get a sense of do we think this is something that can be patched and fixed and just needs to be more clearly explained or somehow are we off on a false track? I mean, I am just not sure where we are.

DR. SHAPIRO: I have a view of that but let's have Bill and then Alta.

MR. OLDAKER: Bernie, I am not sure but one thing I do not understand -- maybe it is just my own lack of experience -- how can it ever be ethical to --

cite me an example of how it can be ethical where you would give some sort of invasive treatment to someone where they had no possibility of benefitting from it but there was a risk to them. How could that ever be ethical? I am talking about not --

PROFESSOR CAPRON: That is Phase I trials and Phase II trials.

MR. OLDAKER: No, you cited the -- I mean, there was a chance it might have worked. It might have had some benefit. Therefore, there was some --

PROFESSOR CAPRON: No, but I am talking about ordinary drug trials, not a cancer drug but an ordinary drug trial where you use normal volunteers. The only one risk.

MR. OLDAKER: But there is some possibility that they could benefit.

PROFESSOR CAPRON: Normal volunteers cannot benefit by definition. They do not have the disease. You do not want people with the disease.

MR. OLDAKER: Okay. All right.

PROFESSOR CAPRON: We do it all the time.

MR. OLDAKER: But what is the risk?

PROFESSOR CAPRON: Some risk that it will turn out surprisingly to be toxic or have some other -- I mean, any time you are intervened with you are taking

some risk. We only do it, I suppose, where there is some good judgment that the preclinical data says that the risk is very small. There is a big argument, Barouche Brody takes the view that we should not do this graduated, slowly graduated up till we get to the -- we ought to start at what we think is probably the maximal dose and if it does not hurt people, go up, and if it does, go down because the other method is statistically more problematic.

DR. SHAPIRO: Alta?

PROFESSOR CAPRON: I mean, that is a separate argument. Yes, we take some normal volunteers in research and we expose them to risk and we think it is acceptable if the risk has been well vetted and they know what it is, and they are normal, competent people who can say yes or no.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: You know, I said something before that I would like to retract because in the course of this discussion, Bernie, which, with you, I find at this point now getting confusing about what we are trying to accomplish. I think actually I now remember accurately the history here and it is nothing that has been discussed so far to my knowledge, although I did step out when I was kind of losing my

concentration.

I think I remember now that this was about a situation which I kept talking about on e-mail in which you have clinical interventions that are accompanied by a pure research component that is piggy-backed on them. And the reaction was, well, then the clinical intervention really is just -- it is about regular medical practice, which means if it is, you know, whatever the clinical intervention is, whether it is standard or comparable to standard then that is fine, and now let's look at the research intervention separately.

Larry began responding on e-mail that he did not see what the role of the IRB was then in evaluating ordinary medical practice. The response to that was, well, it is being kind of rolled into something that has a research component.

And we have seen a lot of these at Wisconsin where you will go out and you will do -- I do not know -- a variety of standard interventions having to do with preventive care for heart disease, the prevention of heart disease. And it -- they roll in a pure research task having to do with interviews about things which are not going to be used for the preventive care but they want to use this population that they have got

there.

It happened at like health fairs in rural areas where they would do blood pressure screening and cholesterol screening and these other things and then they would throw in a research intervention and they would get very annoyed with us, at the IRB, when we would say you have to justify the research intervention and they would go but all these benefits we are giving these people. We are screening them for this. We are screening them for that. And we were like, yes, but that is separate. That is medical care and the piggy-backed research has to be handled separately.

And I think that actually -- if I am reconstructing this correctly -- may be the origin of this separation into having one thing to not societal benefits but purely to whether it is ordinary practice or not.

So I have a feeling that we need to maybe back away from this language which is trying to roll too many things up together too efficiently. It is trying to put -- pack too many things in there at once and talk about the situations. Let's talk about the situation in which you are doing research that is just research with no benefit and then let's talk about a situation in which you are doing research where it is a

clinical care situation with a piggy-backed research intervention.

Now let's talk separately about a situation where you are doing research on a potentially beneficial intervention and then let's finally talk about research that involves multiple components that are being packaged together and that may be an easier way for us to handle it because we will be able to think about it situationally instead of trying to find language that we can then -- from which we can then derive the situations on the application of the rules.

DR. CASSELL: I am going to Wichita, among other things, to talk about NBAC. To paraphrase an old joke I am going to say, "I am from NBAC, we are here to make things simpler."

(Laughter.)

PROFESSOR CAPRON: Do you carry a good life insurance policy, Eric?

DR. COX: Send us a tape.

DR. SHAPIRO: That is right.

Okay. I think -- I mean as I look at Recommendation 3.1, I am going to have to think more carefully about the implications of all this. I am not sure but I am convinced about the point that Alex

started out with here, namely that there has to be some limit on the first of these and that societal benefits are never totally irrelevant.

Now the balancing of these and the weighing of these is an issue we have to confront in the text because we are worried about a particular problem and my intuition tells me that the structure really hangs together if you deal with it appropriately but I have to think it all through. I am not -- I would not say that absolutely yet but I just have not thought it through so let's just leave that right now.

I think we did -- but let me just ask is there anything further on the next recommendation, which is 3.2?

What about 3.3?

Arturo?

DR. BRITO: The proposed -- I think it is the proposed 3.3. Concerning the words "competent" in here. This goes back to -- I am not sure it is time to deal with this but it is just what I -- I will mention this now. This goes back to Alta's suggestion earlier about making this report deal with competent participants or not. And whether we decide to or not, it is going to change the -- some of the implications of the way this is written now, which I have mentioned

before but I just want to make that clear now.

DR. SHAPIRO: We will address that issue as a general issue tomorrow, the first thing tomorrow, and I understand it will have implications on a number of spots depending on what we decide.

DR. BRITO: Okay. And again --

DR. SHAPIRO: And here is one of them. I think you are right.

DR. BRITO: I, by and large, like this proposed recommendation better than the former one, though, with that questionable exception.

DR. SHAPIRO: Other comments on 3.3?

PROFESSOR CAPRON: You also had another comment about this should require versus should require.

DR. BRITO: Right, and I agreed with the change in there.

PROFESSOR CAPRON: Okay.

DR. BRITO: Even though I think it is more than just a simple editorial change, I think it is -- that is the substance.

DR. SHAPIRO: We may have to reflect some more on the text with respect to that.

Other comments?

Okay. What about 3.4? It is really 3.4 and

3.5 now with these proposals. Are there any questions about that? Okay. 3.6?

PROFESSOR CAPRON: What happened in light of our discussion earlier? Are we dealing with this or not? A loss of capacity?

DR. SHAPIRO: Well, I think that is -- we are going to have to come back to this tomorrow. I do not consider this fully dealt with because the other issue which we are going to have to start in the morning is going to impact in various spots here depending on what we decide. So I just want to do that in the morning when we are thinking as clearly as possible and also give us some chance during the evening to think it through.

PROFESSOR CAPRON: We are on 3.6 then?

DR. SHAPIRO: 3.6, yes.

PROFESSOR CAPRON: I have a question.

DR. SHAPIRO: Alex and then Alta.

PROFESSOR CAPRON: This goes to the existing regulations but you can help me because it is in our recommendation. We say that there should be regulations permitting the waiver of informed consent process involving the use of existing identifiable data if all of the following five criteria are met. And the second of these is the waiver will not adversely affect

the rights of the participants.

Now what does that mean?

PROFESSOR CHARO: Oh, God, Alex.

PROFESSOR CAPRON: I mean, why do we say it if it is --

PROFESSOR CHARO: We went around this so many times with the HBM. My best recollection is that we decided that there are places in state law and potentially in federally law that give people specific rights with regard to specific kinds of information.

For example, if the patient privacy act were -- regulations were ever issued, patients would have been given federal rights with regard to their medical records in certain ways and so this --

PROFESSOR CAPRON: Well, okay.

PROFESSOR CHARO: -- would not be usable if they had elsewhere been guaranteed certain rights.

PROFESSOR CAPRON: That is what -- I understand that. Then what we mean is the waiver is not prohibited under other guarantees of rights. I mean, to say the waiver will not adversely affect the rights -- what does that -- it is --

MR. HOLTZMAN: I think that is a great idea.

PROFESSOR CAPRON: Do you see what I am saying?

MR. HOLTZMAN: Because if we are addressing anything in five --

PROFESSOR CAPRON: Yes.

MR. HOLTZMAN: -- it is those other kinds of rights.

PROFESSOR CAPRON: Exactly.

(Simultaneous discussion.)

DR. SPEERS: Will you say it again, Alex?

PROFESSOR CAPRON: The waiver is not otherwise prohibited by guarantees of rights.

PROFESSOR CHARO: Right, either state or federal law.

PROFESSOR CAPRON: Yes.

PROFESSOR CHARO: International law.

PROFESSOR CAPRON: The law.

PROFESSOR CHARO: International.

PROFESSOR CAPRON: Yes.

PROFESSOR CHARO: Other points on 3.6, Harold?

DR. SHAPIRO: Of course. Yes, Alta, and then Trish.

PROFESSOR CHARO: Two things. First, just as a tactical move, it might be better if instead of saying that NOHRO is going to do this and NOHRO is going to do that, that we say that, you know, consent requirements should be waived or, you know, it should

be possible to waive consent requirements if the following criteria are met because if NOHRO does not exist I still want to see if we can send a signal. That is tactical on --

PROFESSOR CAPRON: Federal regulations should.

PROFESSOR CHARO: Whatever. But more substantively on 3.6, when I read this I feared that this was then going to suggest that this is the only situation in which consent waivers would be permitted and I did not expect that was the intent of the way it reads. It has that flavor and so I wanted to just make sure that we clarify that we believe that consent can be waived in a variety of circumstances and one of those circumstances, which has been poorly understood until now, is this one. Right? Because otherwise by implication we are repealing all other consent waivers for all other situations.

PROFESSOR CAPRON: Involving the use of existing identifiable data?

PROFESSOR CHARO: No, involving other situations that do not have to deal with using data or tissue.

PROFESSOR CAPRON: Well, but that -- this to me can be read to say where you are doing studies involving X you can waive if the following criteria are

met. Where you are doing a study that observes people in public spaces or something you do not worry about informed consent it does not fit this because it is not identifiable data.

PROFESSOR CHARO: If I am the only person who is at all misled by this then I happily withdraw the comment. I --

DR. SHAPIRO: I think it does refer only to this, Alta. That does not mean to say as we go through the text and talk about it we cannot give some indication along these lines and so I think we should try to do so. Just because a case -- we are never the only ones. Whatever we think, we are never the first or the last persons to think that way so I think we should take some cognizance of that.

Trish?

PROFESSOR BACKLAR: I just want to say that in case we do not end up doing this on competent people back at 3.4 -- maybe I am missing something but I do not know why one has participants either do not have or have lost the capacity. I would have thought do not covers it adequate. I do not know why you cannot just say or lost.

PROFESSOR CAPRON: Never have or have lost. I mean, we do not need to say it.

DR. SHAPIRO: Yes, that is right.
(Simultaneous discussion.)
PROFESSOR CAPRON: It is at this time that it is relevant.
PROFESSOR BACKLAR: Yes.
DR. SHAPIRO: I agree with that. I agree.
(Simultaneous discussion.)
DR. SHAPIRO: Anything else on 3.6?
MR. HOLTZMAN: Again, perhaps it could be lost in the course of the study.
(Simultaneous discussion.)
PROFESSOR BACKLAR: It is not very clear.
MR. HOLTZMAN: I am just thinking you might want to think about that. You know, you can think about actually the text -- the consent is a process.
PROFESSOR BACKLAR: And that would look after consent --
(Simultaneous discussion.)
DR. MIIKE: It is going back to the capacity report where we dealt with people who gave up consent early on and then later on --
DR. SHAPIRO: Any other comments on 3.6? On this -- I do not know which way you are following along. Some of these numbers change as we go through depending on what you are following along but the short

recommendation 3.7, which I think is now 3.8 in the draft chapter, which talks just about reducing threats of privacy and breaches of confidentiality.

(Simultaneous discussion.)

DR. SHAPIRO: I am sorry. I did not hear you.

PROFESSOR CHARO: It is a typo.

DR. SHAPIRO: Okay. Again if you are looking through the chapter we are really on 3.8 now if that is the -- working along or 3.9 in the listing. Excuse me. It is the other way around.

PROFESSOR CAPRON: Right. 3.9 in the chapter used to be --

DR. SHAPIRO: Any comments or questions? Yes, Bernie?

DR. LO: A minor point. Elsewhere we sort of make the recommendation to be sure to issue guidance and here we are just saying should examine an option. Is that -- are we trying to signal something here or do we want to make it more consistent?

DR. SHAPIRO: This is examine options for strengthening confidentiality protections.

DR. LO: Other places we tend to say should issue guidance regarding --

DR. SHAPIRO: My view is we were not trying to say anything there and we perhaps should make it

consistent but maybe this -- I am mistaken on that.

DR. LO: Because issuing guidance is a little strong here.

DR. SPEERS: Just the history on this was originally it would have to issue guidance and then following discussion among commissioners we weakened it to looking at -- to examine options because this issue of providing confidentiality protections is fairly complicated with mandatory laws that require reporting and how certificates of confidentiality would play into this and so on. So that is why the words were changed.

DR. SHAPIRO: How do people feel about that? This is not a huge point but how do people feel about it?

I do not know how you feel, Bernie. I would actually prefer -- I do not remember the history of all this and I do not remember the discussion but I actually prefer the guidance. So unless there is objection to that why don't we just make it consistent.

Okay. We now have a series of --

PROFESSOR CAPRON: Can I then ask how --

DR. SHAPIRO: Yes.

PROFESSOR CAPRON: -- will 3.8 and 3.9 differ?

PROFESSOR CHARO: Which 3.8 and 3.9 are you talking about?

PROFESSOR CAPRON: The ones in the report on page 47 with the revised version because we will then say should issue guidance on 3.8 regarding how investigators can reduce threats to privacy or breach of confidentiality and should issue guidance for strengthening confidentiality protections in research. I mean, is there a difference between reducing threats to privacy and strengthening protection? I mean, don't you reduce threats by strengthening the protections? Can't we then collapse this into one idea if that is all we are saying?

DR. LO: I think the new 3.8, which is two lines is a lot easier to read than the new 3.9. Why don't we put 3.9 in the text saying to issue guidance that we realize these are difficult issues here, blah, blah, blah, rather than making it a whole recommendation.

PROFESSOR CAPRON: In other words, take 3.9 and turn it into commentary on 3.8?

DR. LO: Right.

PROFESSOR CAPRON: Yes, one way you reduce the threats is to --

DR. LO: (Not at microphone.) To study confidentiality --

DR. SHAPIRO: It seems very reasonable to me.

PROFESSOR CAPRON: The only way that 3.9 goes beyond is that one option the office could come up with would be either regulations or legislation that would actually extend legal protections against unauthorized releases and that would be more than simply guidance. In other words, there would be legislation saying that where you are studying X, Y, Z, this protection is built in and extend the confidentiality -- the scope of certificates of confidentiality to new areas of research or something.

Now that can still be in commentary but you would have to realize -- it would seem to me that that goes beyond what 3.8 deals with which is only within the existing regulations telling IRBs and investigators how they can reduce threats to confidentiality in the way they conduct research within existing rules.

There is a slight nuance and difference. I just thought we could fold them in together but that is different than eliminating one line.

DR. SHAPIRO: Okay. Let's try some options here. I think that is -- I am not sure which way to go but I think some change is appropriate here.

Now the next section of this chapter is the whole set of issues that deal with vulnerabilities and it starts a long section. I do not know how long it is

but it is long.

And all the recommendations, save the last one, in this chapter deal with that and it is not clear to me that it is useful for us to discuss that at this stage until we have resolved some of the other issues but I am certainly happy to take any questions, observations that you may have at this stage that would help us with our discussion tomorrow morning regarding whether we are going to deal only with -- the report may or may not deal only with the competent patients or not. That discussion still has to come. So that is how it appears to me but I am glad to take any other observations now.

PROFESSOR CHARO: Because I found what is now Recommendation 3.10 in the draft to read -- I found it be kind of internally somewhat contradictory. I would want to -- I would like to suggest that we have a positive statement that just means all of this. Either here or elsewhere. And the positive statement would be that research should take place with broad populations that represent a range of people in society unless there is a special need to work with a specific subpopulation.

So that we can get on the table first and foremost the notion of inclusion, justification that

for research results to be generalizable to the general population they generally have to be derived from a sample of the general population so that to maximize societal benefit one must design the research to be inclusive.

Then we say -- then we move into the discussion that started earlier and we will continue tomorrow, when you are doing your research there will be certain situations that create vulnerabilities. Here are some of the situations and here are some of the solutions. When you are designing projects with subpopulations, right, those subpopulations should not be used unless the research question is one that is relevant to that subpopulation particularly and that takes care of the problem of the targeted vulnerable groups.

I think it creates a somewhat cleaner line of distinctions than we now have where we seem to be giving on one hand but taking away with the other in the same rec.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: Yes. I had marked the last two sentences here as raising that question. I wanted to go -- I think it was Bernie's example, though, before about the nursing home patients and if you

assume that nursing home patients are geriatric patients but they are geriatric patients who are frequently cognitively impaired and certainly institutionally impaired and they are dependent upon the institution in various ways, would it be a contradiction of the last sentence to exclude them if the question is a new drug which you want to be able to use in the adult population, including people over age 65 or 70, but where you do not have any reason to think that nursing home patients as opposed to other geriatric patients have different metabolism.

So you would say they do not make good subjects because their ability to give autonomous choice is situationally and perhaps cognitively limited. I just do not know if that sentence says, no, that would be disproportionately excluding people with vulnerabilities from research and the only reason would be because they are vulnerable. I mean, there is not a separate reason. It is the very thing that made you be worried about them.

DR. SHAPIRO: It seems to me -- I mean --

PROFESSOR CAPRON: I cannot answer an example.

DR. SHAPIRO: Right, I do not have an example either but this issue has come up a number of times now in various contexts today and at least it appears to me

that you would not want to disproportionately exclude them if there was something -- you believed there was something to be learned by including them. That is if you believed in the example you gave.

PROFESSOR CAPRON: That is what I am saying. In my example there is nothing to be learned by including them. They are --

DR. SHAPIRO: I think they should not use them in that case. That is my view.

PROFESSOR CAPRON: Because they are vulnerable.

DR. SHAPIRO: Because they are vulnerable and we do not need to. There is no benefit to them or to us.

PROFESSOR CAPRON: They -- if the drug works out it can be prescribed to them with no limitation.

DR. SHAPIRO: That is right. That is my view. I think we have a different view from the West Coast, the Midwest or wherever it is Wisconsin.

PROFESSOR CAPRON: Northwest.

PROFESSOR CHARO: Wisconsin? It is in the Great Lakes region.

DR. SHAPIRO: Great Lakes region.

PROFESSOR CHARO: We do not call it the Midwest if we are from New York. We call it the Great

Lakes region. Kansas is in the Midwest. Ohio is in the Midwest.

DR. SHAPIRO: Midwest always seems to be father west than wherever you are.

(Laughter.)

PROFESSOR CHARO: Harold, I am comfortable with this example only because of the cognitive impairments but if we were talking about competent people who are in an institutionalized setting I would want to approach it slightly differently.

Now part of it is because we often have jumped to the conclusion in the past that there is no differences among people and have excluded large numbers of people and women is the classic example. And, of course, we have now come to understand that that assumption was not well founded. In some cases there are real differences and in some cases there are not, and we did not have enough data to really know when -- which is which and when is when.

But more -- probably more honestly it is because I think I share with Rhetaugh the instinct that more harm than good is coming from this kind of blanket exclusionary policy and that it -- it has invited an attitude of ignoring people and it does not serve their interests in the long run.

Now, of course, part of that is because I guess in some cases you do find real differences. I would be happy to talk about it further but let's just say I do not worry so much about the nursing home residents or the prisoners but I am just waiting for the next groups on the list to be named.

PROFESSOR CAPRON: Pregnant women. Pregnant women.

(Laughter.)

PROFESSOR CHARO: Or even the nonpregnant women. The might get pregnant some time in their lifetime women. Right. The do not speak standard English people. The people who have a strong suntan people. I mean, it is just everybody is on the list.

DR. DUMAS: Red heads.

PROFESSOR CHARO: Well, red heads, no, they are not vulnerable. They are just lucky.

DR. SHAPIRO: All right.

(Simultaneous discussion.)

DR. SHAPIRO: Bernie?

PROFESSOR CAPRON: Left-handed people.

DR. SHAPIRO: Bernie?

DR. DUMAS: Yes, because people automatically assume that they are fiery and they are impulsive --

(Laughter.)

DR. SHAPIRO: Bernie?

PROFESSOR CAPRON: I have an N of one in my house that fits that.

DR. SHAPIRO: Bernie?

DR. LO: Well, I mean, Alta, I can see where you are headed but I mean nursing homes and prisons are total institutions and there is a history of real abuse. The problem with nursing home patients is not that they have been under studied, they have been roped in as guinea pigs when, you know, there is no way they could say no and their surrogates -- studies have shown their surrogates do not make decisions on what is best for them.

So I think using the same arguments we used in the capacity report, these are situations where there has been a history of abuse that called for, if not regulations, calls for regulations. And these continue to be institutions where, you know, you can say include them in the research but the nature of nursing homes is such now with care cut backs, funding cut backs that it is going to be very hard to get meaningful, informed consent in that kind of environment.

So you are balancing potential harms to other people who are sort of a little further down a slippery slope versus real harms to people who are utterly

dependent on an institution.

DR. SHAPIRO: Marjorie and then David, Steve.

DR. MESLIN: Larry.

DR. SHAPIRO: Larry is next. You are on the list here.

DR. SPEERS: I was just going to give some examples of the opposite situation where individuals who are potentially vulnerable are included in research because it is convenient to do so. In addition to the institutional setting, research that is done in free clinics, for example. If people want to study sexually transmitted diseases, the easiest way to go do that is to go to the STD clinics and study the individuals who go to those clinics. But not everyone who has STDs goes to free clinics but it is easier to do that. If you want to study unintended pregnancy, again going to a reproductive health clinic, it is easier to do the study there.

What happens is if you go to those kinds of settings is you have people who are often of low income, of low educational attainment, they may be minorities, you have a lot of other factors that enter into the study. So the risk is the -- may be the opposite of individuals are being included disproportionately because of the ease of studying

them.

DR. SHAPIRO: Okay. Larry noted to me that he has had his hand up for a long time and I probably did not see it right away. I am going to go to Larry next.

DR. MIIKE: I just want to reiterate this issue about recommendations 10, 11 and 12. I really think that the capacity part should be way back with 4 if we are going to have it at all because it is not peculiar to vulnerable populations in general. It is peculiar to the capacity of people.

And so if we leave it the way it is, 3.11 looks very weird. All of a sudden we have to come out and say, oh, by the way, local review is okay or local IRB review is okay for people with vulnerable -- even when they have greater than minimum risk. So it is just that -- the logic does not sound right to me and it just should be -- it is not about all vulnerable populations. It is about the capacity issue and it should really go back by 3.4.

DR. SHAPIRO: Okay. David?

DR. COX: So I am sitting here this afternoon as a researcher thinking about how I am going to use this stuff. Totally opaque. Because what is happening is the basic principles that we started off this morning talking about, okay, we are not dealing with.

What we are doing is that we are getting into the real nitty gritty of exceptional situations.

Now I do not mean that these ultimately are going to come out. Okay. And they are the gray areas that are going to be adjudicated but we are dealing with the gray areas without sort of laying out what the mean highway is for people.

Now maybe we are going to lay the main highway out but I will say in this very issue of vulnerable individuals is that the climate is really different, folks, than it was ten years ago or even five years ago. So we are not in the situation anymore where the -- sure, there will be the outlier person that will go and misuse nursing homes or prisons. That is not the situation we are in anymore. We are in a climate where people are not doing anything because they are scared to death.

So it is a very different climate and what we cannot do, I think, is make regulations and rules based on ten years ago. We have to sort of -- and we cannot even make them on today because by the time they get implemented they will not be relevant either.

So the -- to look at these basic principles and the ones that -- if we start making groups that -- we will never quit making groups and everyone will

spend all their time on the groups instead of looking at, you know, who is really at risk. It will be do I have the right groups or not?

So I just -- I take this as an example of all of these. These are all important issues but I think that they are not nearly as important as laying down what the fundamental principles are behind these different things, which are in here. Right. But for us to really spend some time clarifying those.

DR. SHAPIRO: Well, we certainly intend to do the latter and I think, David, one of the attempted characteristics of these set of recommendations, whether successful or not, is to provide a mechanism where it could be much more flexible ongoing.

DR. COX: I quite understand and I am keen on that but what I am doing is reflecting. I am putting myself in this different setting.

DR. SHAPIRO: I understand.

DR. COX: And I think that as a user, these discussions that we are having are very, very subtle points that are going to be totally missed by most users but they are going to be picked up immediately by the people that are interested in using them for not necessarily good reasons.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I am struck that I think the problem we are running into in 3.9, I suppose it is now new 3.10, is in fact we are trying to use a formulaic kind of formulation if you will and it is casting the net too wide and too narrowly all at once. And I think consistent with where Alta was going and David about the principles, what is really at stake is if you go back to your basic principles about beneficence protection, what we -- the research environment has changed and there are still cases where we are worried about institutional people being used as guinea pigs and it is also the case where we are worried about people being systematically excluded from trials and then lo and behold effectively the research takes place in the marketplace because it is prescribed off label, et cetera, et cetera.

So I am wondering if we just could not come out and say it here. Right? That when you -- instead of these safeguards -- you know, these safeguards should be incorporated, we then go generally participants with vulnerabilities should not be targeted and maybe that is where our problem starts.

We maybe should say, you know, what this means is, you know, people should not be used as guinea pigs because it was just easier, cheaper, faster, all right.

Help me out here, guys, with things? Principles of justice, right. That principles of justice -- that if, in fact, the goal was to have this applicable to a population it should be generally represented in the study. And just start to spin them out there that way. It might work.

DR. SHAPIRO: Thank you.

Other comments?

DR. COX: Harold, I am quite keen on that because I understood what Steve said and that -- I mean, not that I have not understood these other points but they have to be crystal clear because when people are working --

PROFESSOR CAPRON: David, also, just for the record, more biomedical research with human beings is going on today than ten years ago. It may be that high class university investigators who are scrupulous and whose IRBs carefully look at this are more inhibited and feel antsy and we should not contribute to that. That is to say we should give them clear guidance so that they do not just feel worried and think that they can do nothing.

And maybe the real problem is contract research in private doctors' offices but there is more of it going on than ever. So the notion that somehow

there has been a huge inhibition of the research process, I think, is wrong. Maybe of good research, maybe of -- you know, really path breaking research but there is a lot of drug research going on.

DR. COX: Indeed, Alex, but think of it in the context of what this report is going to deal with. It is primarily federally funded stuff. Hopefully, other funded stuff, too.

PROFESSOR CAPRON: Well, I mean the whole point of this is to say --

DR. COX: Hopefully that happens.

PROFESSOR CAPRON: -- principle one is everybody.

DR. COX: Yes. But the -- and so there is no question you want the rules out there. I think the climate is fundamentally different now, though, than it was five years ago in terms of the fact that people do not make jokes about this in public anymore.

And five years ago everybody made jokes about this in public. It does not happen anymore in the research community. So now at cocktail parties people talk about how they are scared that they are going to get shut down, not about how stupid it is. That is a fundamental change. A fundamental change.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: If I can just kind of go back to this. My goal in what I was outlining before was indeed to handle this nursing home example by saying first on the one hand that you need to have a broad section and, second, if you are dealing with subpopulations where you are concentrating one kind of person, you have to have a justification for it, which would seem to invite having a couple of nursing home residents in your sample but preclude having your entire sample be made up of nursing home residents unless you could provide justification for why this research is peculiar to nursing home residents. So that was my goal, although it does not -- it is not clear that it accomplished -- I was accomplishing that goal because of the response I got back.

I must say, though, that even though I still feel like that might work, I am anticipating an additional problem -- sorry, guys -- that we might or might not want to at least acknowledge and anticipate, and it is in conjunction with multicenter trials. Because if you have, as we growingly increasingly do, a sponsor who has work going on in six different universities, one thing that may very well happen is each university tends to have a particular population it is working with so that the entire population across

all six together represents a cross-section but they are chosen for specific reasons. This one is an urban campus and has this population and this one -- but your doctor with the contract research, that is exactly what is going to happen.

He or she is going to wind up getting paid to go in over and over to that nursing home because this doc is a geriatrician and keep recruiting those people for study after study that is being plugged into a variety of multicenter studies.

We need to know if we are comfortable with that because it is not that you are using them for one study en mass because they are easier, it is that what will happen is we will have a kind of bulkinized research system. I am sure we have all seen a little bit of it in our own institutions in which this has been the way to handle the diversification of the subject population. It has been collaboration with universities in very different settings.

And we need to decide if that is okay, you know, because it will look in the end very much like what it is that disturbs you, Bernie, even though it is not exactly the same situation. It will look in the end a lot like it.

DR. LO: There is the additional issue, Alta,

of the patient's doctor going back to the patient population and recruiting over and over again from the --

PROFESSOR CHARO: I completely agree with you which is why I am saying, you know, reluctantly I added to the list of problems.

PROFESSOR CAPRON: If the reason for the last sentence in the revised version, however it is also inappropriate to disproportionately exclude persons with vulnerabilities from research unless there is some reason, the reason for that is that it is inappropriate if you will end up with results that are inapplicable to that population. That was the reason for saying, yes, you must very carefully recruit in that population and include them so that they do not lose the benefit.

If the purpose of this is to buy into the therapeutic misconception that they are getting gypped from not being in the research, not the results of the research, but the research then I reject it and I would, frankly, say to the extent that you are dealing with a population where the probability is much higher that you are going to get people not giving autonomous consent but either by their mental capacity or their situation being manipulated into this, then you should find other people who are medically equivalent to them

so you can generalize the results who do not have those problems and you should not go to that population. And it is not discrimination against them that they do not get the privilege of being research subjects.

I mean -- and I will write a dissenting footnote if we say it the way it is here unless we make it clear that the reason is that you end up having to do, as Steve said, off label research with the population after it is approved because you do not know if it fits them or not. And that is a separate issue.

You resolve it drug by drug. Maybe anti-bedsore medications are different if bedsores develop at home or in the institutions. Maybe you have to do the research in both places.

DR. SHAPIRO: David?

DR. COX: So, I mean, this issue -- particularly the one that Alta brought up -- is that for purely scientific reasons often times a particular population in these multistudy trials is the best population to deal with that component. You can get it better for a whole variety of reasons. Not just because it is easier to go back to the nursing home but it is pretty hard if for a scientific reason what you wanted to do was look at a distinction between African Americans, Asians and Caucasians. It is pretty hard to

get a stratified sample of all those people in Iowa. I mean, it is not so easy. So if that is what is going to be asked --

PROFESSOR CAPRON: That is fine.

DR. COX: -- then it makes no sense.

On the other hand that you do not want people just going back in for contract research when there is no reason to have it be nursing home people and just have it be because they are the easy people to get.

So I think that this is going to be very hard to write down in rules this way because I can argue both sides depending on the situation and there is no way, I believe, that it is possible to incorporate that into a recommendation.

PROFESSOR CAPRON: We are dealing here with vulnerabilities and institutionalized people are an example of a vulnerable population.

DR. COX: Yes.

PROFESSOR CAPRON: We are not dealing here with the need to have a multi-ethnic population so you contract with the University of Iowa and you also contract with Cornell.

DR. COX: I understand. But my only point is you can deal with the vulnerabilities without having to delineate the groups. That is all I am saying.

DR. SHAPIRO: On this particular issue, which is the last sentence in whichever number it is, 3.10 -- I keep forgetting how these numbers --

PROFESSOR CAPRON: It is 3.10 now.

DR. SHAPIRO: I mean, I agree with Alex's analysis. I understand the point you are making, Alta, and I think that has been a problem in the past but as I balance the problems and so on it is just come down on the side of the general presumption. But we can talk about this some more and see how the text looks when we put it together.

Well, I think we have taken our discussions as far as we are going to take them this afternoon so let me thank everyone for being here. We will have some pretty important discussions tomorrow morning and, as I said, we only have -- what time do we start tomorrow, Eric?

DR. MESLIN: 8:30.

PROFESSOR CHARO: Do we want it to be 8:00?

PROFESSOR CAPRON: 8:30 it says.

MR. HOLTZMAN: It is usually 8:00 for the second day.

PROFESSOR CHARO: It usually is but the agenda said 8:30 but 8:00 is fine.

DR. SHAPIRO: How do people feel about meeting

at 8:00 versus 8:30? Does anybody have any preference?

PROFESSOR CAPRON: We will acquiesce. Do we have a preference?

DR. SHAPIRO: Let's try to meet as close to 8:00 as we can because we are going to have to adjourn somewhat earlier than indicated on the agenda given all kinds of issues so that we probably will be through here sometime between 11:00 and 11:30. So let's get together as close to 8:00 as we can tomorrow morning.

Thank you all very much.

(Whereupon, at 5:02 p.m., the proceedings were concluded.)

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