MEETING OF THE HUMAN SUBJECTS SUBCOMMITTEE OF THE NATIONAL BIOETHICS ADVISORY COMMISSION

Sunday, November 23, 1997

National Institutes of Health
9000 Rockville Pike
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Bethesda, Maryland

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I N D E X

P R O C E E D I N G S

CALL TO ORDER AND REMARKS

DR. CHILDRESS: Let me welcome subcommittee members and others. I am glad that all of you could make it and make it this early. Let me also welcome others.

We will have an opportunity for public testimony at 11:15. We had, I think, two people who have indicated they would like to testify at that time. If there are others, please indicate to Pat Norris or someone at the desk outside and we will be glad to then adjust the time to make sure that we have enough allowed to accommodate everyone.

Before I say something about our agenda today let me see if Dr. Shapiro would like to say anything at the outset.

DR. SHAPIRO: No. Just to thank everyone for their continuing efforts and to wish us good luck today.

DR. CHILDRESS: Thanks, Harold.

MR. CAPRON: Did you see the poster that was up in the elevator talking about balancing family life and work? I am sure it had nothing to do with holding these meetings on a Sunday.

DR. SHAPIRO: Why would you raise that now?

(Laughter.)

MR. CAPRON: No, it just was of interest I

thought.

MS. CHARO: Some of us would like to have the time to create a family. This does not look like a fertility clinic.

(Laughter.)

DR. CHILDRESS: Are you restricted to a particular date on that on the record, Alta?

(Laughter.)

DR. CHILDRESS: Our agenda today is a very full one. Let me make a few observations about it. First, we want to determine where we are and what else we need to do over what period of time to produce a report on decisionally impaired research subjects.

For the consideration of the commission as a whole and that will be a stage we have to think about when we think we are ready to send something to the commission as a whole, at what point in the process, and in talking to Dr. Shapiro the idea emerged that probably it was best as soon as we had some fairly clear recommendations even though the rest of the report might still be evolving. We will think about that towards the end of the day as we consider this very fine draft that Jonathan Moreno has developed in response to the discussion last time and in response to individual questions and criticisms and suggestions after the meeting.

In addition to going over that very carefully today we will hear from some other researchers with particular focus on imaging research and everyone should have received in addition to the testimony we will hear today -- should have received written testimony from Dr. Bruce Cohen that was faxed to everyone on Friday. He could not join us.

Those that are traveling obviously did not get that.

DR. DUMAS: I thought I got two pages of it.

DR. CHILDRESS: Oh, two. Okay.

DR. DUMAS: Yes.

DR. NORRIS: I have copies.

DR. CHILDRESS: We have copies here. All right. And it will be helpful to look at that at some point. It is relatively brief but also very, very helpful. He regretted he could not join us and would be glad to at some later point.

And then we will have public testimony today but that will be on a broader -- that is it will go beyond the research involving decisionally impaired subjects.

And then second we need to determine where we are and what we need to do to finish and when we can finish our report on federal agency protection of human subjects in research.

One important point on the basis of discussion with staff and with other commissioners and with Dr. Shapiro, we do not expect to complete this report until the early months of 1998. The staff has done a great job in obtaining important information for us but we still need as a commission, and I hope we will make progress on this, this afternoon, to determine the exact findings and appropriate recommendations.

In addition to that we need, with Kathy Hannas' help, she has agreed to work with us, and others, to recast and rewrite the report in order to attend to the overall picture. So that will be a stage that we will move to after the discussion this afternoon.

In connection with that report and more generally we will consider today, this afternoon, two thorough draft contract papers, by Charles McCarthy and John Fletcher, on the federal regulation of human subjects research with particular attention to the location of an OPRR-like mechanism within the federal government. This grew out of a point and suggestion that Alex Capron made and I think. And I think that we fortunately have two very thorough and interesting papers. We will have a paper later by Tina Gonzalez on whether this mechanism could function to regulate or to provide oversight of nonfederally funded research.

We will also hear this afternoon from Joan Porter about the period between the proposal and the adoption of the common rule to try to understand better the obstacles that were in the way of the implementation of the common rule that may still endure. Some of those are addressed in a draft report but there may well be others and this grew out of some suggestions that Alta Charo made.

So that is what we are doing today with some thoughts at the end about our next steps but also along the way in relation, for example, to the report on decisionally impaired research subjects talk about next steps. So at the end of today we are simply pulling together some of the discussion we had earlier.

That is our agenda. Any comments about that agenda?

DR. SCOTT-JONES: Jim, I have a question.

DR. CHILDRESS: Sure.

DR. SCOTT-JONES: This is just about materials that we were sent prior to this meeting. There was a note that we get a report on the survey of federal agencies under separate cover. I did not get that.

DR. CHILDRESS: Right. But my recent mail said that nothing would be provided until we arrived and you should -- were you at the hotel last night?

DR. SCOTT-JONES: Yes.

DR. CHILDRESS: You would get it at the hotel last night.

DR. SCOTT-JONES: Rhetaugh got something but they told me there was nothing for me.

(Simultaneous discussion.)

DR. CHILDRESS: I did not get it and I do not think anyone got it in time to read it and that was not the point but rather to have it available before this morning but we have copies available here.

DR. SCOTT-JONES: If I could get a copy that would be great.

DR. CHILDRESS: Okay. See if we can get copies made then.

DR. DUMAS: Do you want my copy? Here it is.

DR. CHILDRESS: If you have it handy that would be great.

DR. DUMAS: Yes.

DR. CHILDRESS: You are trying to get rid of paper, I believe.

DR. DUMAS: I am.

(Laughter.)

DR. CHILDRESS: So this afternoon the discussion will not focus so much on a document but rather on the way in which Bill and the staff have developed a

more narrative approach and descriptive approach to some of these materials in order to respond to the questions that were raised last time and the concerns that individuals have expressed since then about how to make sense of the report as a whole. So that is what we will be doing this afternoon, looking at, in a very open way, of the findings and recommendations in these few pages he provided. There are not very many. They come largely from factors two and three and basically provide that kind of a summary, and Bill will help us do that this afternoon.

The staff working on the federal agency report circulated it to the Interagency Human Subjects Committee this week for discussion and then met with the committee of the draft document so part of what will be reflected in the discussion this afternoon will be the kinds of concerns that were expressed at that point as well.

Any other comments or questions?

All right. Let's start then with the report on decisionally impaired research subjects and again as I mentioned we are very grateful to Jonathan Moreno for his very responsive revision, especially trying to deal with the points raised last time in the meeting but then also subsequently by individual subcommittee members.

I have asked subcommittee members to take

primary responsibility for kicking off the discussion of the same topics in the draft report that we looked at last time but before I turn to individual subcommittee members let me ask Jonathan if he would like to highlight some of the major changes in the draft document and then we can talk about the other matters.

REPORT ON HUMAN SUBJECTS SUBCOMMITTEE ACTIVITIES AND DISCUSSION

UPDATE AND OVERVIEW

DR. MORENO: It has been too long and I do not remember the different design between this draft and the previous one in detail but the major difference is that the risk discussion was moved around as people recommended. There is a new first chapter that highlights some of the issues that people got out of the upfront of the draft and then also I hope changes the way in which the other material that is now chapter 2 is introduced and the introduction of that material is also a bit different. And various language and interpolations of members have been introduced throughout.

DR. CHILDRESS: Any questions for Jonathan about this draft before we move into the substantive discussion?

Okay. All right. Let's then first of all think about the overall structures, direction and tone of

the report. You have already heard from Jonathan some of the changes in the overall structure. I have asked Trish, Laurie and Alex to address these points but this is for everyone. These people are just to get us started on the discussion.

Trish?

MS. BACKLAR: I have a number of points. So many that I cannot find them all. I do want to start right away with something that may be an old problem that was not corrected and very specifically on page 64 it says, "This report will concentrate on the question of whether research should be permitted on those found to be decisionally incapacitated rather than those at risk for decisionally incapacity."

I am sorry. This just blew me away again. I thought am I reading this correctly or maybe this is an old problem. I just need to know again very clearly who we are addressing because in the beginning you did use that little formula that I gave you about the different groups of people. But as we progressed through the paper I am not really certain who we -- what population we are addressing. It is not that I have any doubt. I knew this had to be a mistake but I wanted to be reassured.

DR. MORENO: Yes, of course.

MS. BACKLAR: Thank you.

If I have anything to say overall it is this fact that I am not quite certain who we are addressing other than I am quite certain that we are addressing people who are decisionally impaired but this is such a large group that each time I would find something I was wondering who that person was -- who that -- in that population who it was. Was it going to be people with Alzheimer's who were no longer -- who were incapable of decision making? Was it going to be people who could consent but might lose -- I do not need to go through all of those. That is point one. I am a little concerned about that aspect of the paper.

The other thing that was never really clarified for me --

DR. CHILDRESS: Excuse me. Since I --

MS. BACKLAR: Oh, sorry.

DR. CHILDRESS: Would it be the case that the direction of the recommendations indicates pretty clearly how these different groups will be covered?

MS. BACKLAR: Yes, I am going to get to that.

DR. CHILDRESS: But if that is the case then what we need to do is just make sure that the report moves that way if we accept those recommendations.

MS. BACKLAR: I think that as we go along the way the report is set up in such a way now that we go

bumbling along and then we get to something about the commission. I also want to say something about that. It is not clear enough to me yet which -- we talk about the National Commission and then we talk about the commission and I think --

DR. CHILDRESS: This is -- the commission is always now the National Bioethics Advisory Commission.

MS. BACKLAR: Right. If I was reading this paper and I had never read it before I would be very concerned --

DR. CHILDRESS: Well, that is an editorial thing that will be inserted --

MS. BACKLAR: That is why I am just making that comment because --

MS. CHARO: Directly on what Trish was saying because I think that as I was reading it I was finding in it a wealth of observations but I was also struck by the fact that the graphic box analysis that is very complex as you look at the particular subpopulation of at risk fluctuating currently incapacitated levels of risk of the experiment, therapeutic benefit and possible interventions, and I found that I was wondering if it might make sense to actually break this thing out by specific subpopulations.

It will mean a lot of text will be copied over

multiple times for different subreports but this way focus one report on those who are at risk of progressive loss of capacity and a second report on those who are currently have fluctuating, and the last one on those who are functionally incapacitated to address Trish's concern because I found it all in there but it is true that as we trace examples you are not -- for the sake of editorial purposes you are not going to rewrite each sentence to give an example for each population and yet then it gets hard for the writer and the reader to hold it all together.

MS. BACKLAR: I am very concerned about the people who are going to read this who want to get something useful out of it how they are going to get what -- where they are going to go.

MS. CHARO: Yes.

MS. BACKLAR: Even though one might be able to do that ultimately in the recommendations --

MS. CHARO: Right.

MS. BACKLAR: -- I would like to be guided. I would like for that group of people who we are addressing for them to be guided through in some way --

MS. CHARO: Right.

MS. BACKLAR: -- that is easier for them.

MS. CHARO: Yes. I mean, this is tedious and

it is all there and I doubt you will find that there were any substantive gaps that are revealed by this editorial change although this would help reveal them if they are there and that we will miss them but it might be worth waiting for --

MS. BACKLAR: I also --

DR. CHILDRESS: Does everybody -- Alta just made a contract proposal here. Is this something, Alta, you want to elaborate?

MS. CHARO: I am throwing it out as a suggestion as one way that one might be able to tackle the problem of having so many variables operating all the time throughout the report and you can cut it any way. You could just divide it into research that is minimal risk and therapeutic or you could slice it any way you want but what I am suggesting is that you might need to slice it and have three separate subreports. And by "nature of underlying population" might be one way to approach it because that -- I always find in legislative drafting what you want to do is think about things from the point of view of the user.

DR. CHILDRESS: Let me pose a question though. I guess I would take the view that rather than -- I guess I think the analysis that has been provided by Jonathan and Rebecca is a very, very important analysis and that

there is no need to get rid of that. There is a need to perhaps sharpen that at points and expand it and so forth. But then it seems to me that what you are proposing is a clear, and I hear Trish too, is basically a clear set of recommendations that will tell us now what we have to do with different types of populations.

MS. CHARO: In other words, in the end the recommendations are going to be based on a series of variables having to do with the underlying population and the nature of the decisional incapacity.

DR. CHILDRESS: Right.

MS. CHARO: The nature of the risk, the nature of the benefit, and specific interventions that we might recommend. I think that the underlying analysis for all of those things is already present in here. I have no problem with that. And I think that as a piece of -- I mean, I actually did not find it difficult to follow the analysis. It was just that in the end when it comes to leading up to the recommendations it might be easier to have smaller bite size pieces and that means perhaps a lot of duplicative writing but it does provide you in the end with a series of smaller more focused report followed by recommendation. Here in this case the suggestion is to the underlying population that you are looking at.

DR. CHILDRESS: Okay. Let's get some

response. Alex?

MR. CAPRON: I think I would only be able to respond to this if we at some point today or some other time carefully walked through the report and asked which of the portions are going to be relevant generally and there is really no reason to repeat those and at what point are we dealing with something -- say the advanced directives idea, which is much more relevant to either a fluctuating or diminishing capacity situation.

And it might be to have -- I am not sure what Alta means by separate reports or whatever, but it certainly might be that as we approach the recommendations section that we would have a chapter on this research population and a chapter on this one and a chapter on that one. And as you say within that there might either be some explicit repetition or a full statement and then a briefer recapitulation with reference back as with those who are in diminishing capacity situation are at risk of losing their incapacity so too here with those at fluctuating capacity the device of an advanced directive. In other words -- which has been more fully discussed in chapter 7 or whatever.

MS. CHARO: Right.

MR. CAPRON: But I think in principle what Alta suggested is very sensible and I would just want to

be able, which I am not able to do in my own head right now, to know at what point you really are -- you have to shift to that mode. It does seem to me a good deal of what is in here would not be changed by your suggestion.

MS. CHARO: I mean, I am not the writer and I do not want to try to staff this thing. It is being well staffed already. It is just it is a way of trying to put a little more detail on to Trish's reaction which I think is well narrated but it is all there but by the time you get the recommendations you have covered so much terrain that you can find it difficult to remember which things apply to which situations. So it is really just feedback to the staff about how to handle this difficulty in such a complicated area.

DR. MORENO: I have thought about this as well and Jim and I have talked a little bit about some of this in the margins. Of course, a difficulty in doing it population by population is you have to agree on how to discriminate one population from another and people know better than I around the table that there is a lot of range in terms of capacity and so forth within a single diagnostic group. So you probably are not going to end up being able to do it that way except perhaps by begging the question about what counts as being in this population. Very far gone Alzheimer's, for example. Those you could

say clearly have profoundly diminished capacity. But then what about people who are very psychotic?

So another way to do this, and I think you actually touched on it, and I had done a little fantasy piece for Jim at the beginning before I even started writing anything months ago, taking the recommendations at the end and doing a box but characterizing it in terms of cells for risk group and kind of research, therapeutic and nontherapeutic, a distinction that I know has difficulties. So that one thing you could do is box it that way into those kinds of cells.

You are going to get --

DR. CHILDRESS: That could be useful even as part of the discussion --

DR. MORENO: That would be very useful --

(Simultaneous discussion.)

DR. CHILDRESS: -- to chart it in some way.

DR. MORENO: Right.

MS. CHARO: Yes.

DR. MORENO: That kind of chart would certainly be very useful.

MS. CHARO: Yes.

DR. MORENO: Especially for the endusers as you put it, the --

DR. CHILDRESS: But also for our thinking

process.

DR. MORENO: Right. To understand what the picture -- the universe is that has been created here.

DR. CHILDRESS: Yes.

DR. MORENO: But I am very concerned that the specialists here are going to disagree about, you know, what kind of patient population is going to be suitable for what kind of protection if we put it that way.

DR. CHILDRESS: Would one possibility be to take the kinds of categories that Trish helped developed for the beginning of the report and use those as organizing devices at the end with then a different, say for example, disease categories appropriately falling in more than one as you write a note in the report? Is that a possibility?

MS. BACKLAR: But that is, of course, what I intended about those categories, that they were more open and that people would slip in and out of various ways of --

DR. CHILDRESS: But see raising it this way -- I mean, it is a little different than choosing, you know, Alzheimer's patients, et cetera, et cetera.

MS. BACKLAR: Yes, right.

DR. CHILDRESS: Is this a possible direction?

MS. CHARO: Sure, absolutely.

DR. CHILDRESS: For charting it out then. Do we have an agreement that this is worth exploring both in terms of -- and you are comfortable with Alex's use of chapter rather than report?

MS. CHARO: Yes.

DR. CHILDRESS: And then to use -- try it with the categories of Trish's.

MR. CAPRON: But this might even -- this might be within a chapter framework or Jonathan's and Trish's comments might say, "Well, let's just deal with the issues and recognize that the population is not well enough defined to be segregated by chapter." I am also comfortable with that. I was just responding to Alta's --

DR. DUMAS: My thinking tends to be more in line with what Alex just suggested. I have been in conflict about how best to focus this and if we try to focus it on types of patients, levels of impairment, I think it is going to be more confusing. So I would suggest that we try -- I think there is a need for focusing that and that we consider doing that by issue, by type of concern or condition that we want to see considered in relation to whether these patients should be involved in research or not.

DR. CHILDRESS: Eric, sorry I forgot to come back to you and I promising I would.

DR. CASSELL: I want to throw a little monkey wrench and I am disturbed in part because when we do this the implication is that there is a category, by far the largest one, in which people have no trouble making decisions or are not at all impaired in making decisions and they can consent, weighing the benefits and the risks of what is being proposed, and then there are these impaired subjects. But the study that one of my research assistants is now carrying out shows that virtually everybody in the hospital has impairment to some degree. Sometimes it is very subtle but the sicker they are the more impairment they have.

We all know, to add further, that the standard consent form which meets that business of ordinary healthy people can make decisions, we all know that that is thought. So while I think it is fine to have certain categories because they help people fix their minds on something we should not let it come out with the implication that the other folks are all fine and that we can go back to the kind of decision or the kind of consent form we had in the past.

In a sense I think one of the things this should help us do is move forward with all consent. It changes the responsibility of the consent, the person obtaining consent so that the possible impairment by the

environment is recognized in almost everybody.

Now if you say, "Well, what does that mean, Eric?" I really do not know the answer to that. But if you say -- I say to you, "Well, what does it mean that a person with Alzheimer's is prospectively incapacitated? How are you going to change what consents you get from them?" I think you are equally troubled by that.

DR. MORENO: I have, by the way, introduced some language to satisfy your concern about this point, Eric. I have not -- I did not enlarge on the question of -- the larger questions of the inadequacy of consent processes but obviously we would be happy to do that if that is what folks wanted.

DR. CHILDRESS: Alta and then Diane?

MS. CHARO: I do not disagree with what you said, Eric. I agree completely but I do -- not only was there some language that certainly can be beefed up already in there to address this but I do want to continue to recognize a significant distinction between research on people who have illnesses whose primary effect is to interfere with their cognitive or emotional capacities to make decisions and people whose illnesses have that as a secondary effect.

I think there is a fundamental difference because of the phenomenon of them doing research on people

-- when you are doing it on people with an illness whose primary effect is, in fact, interfere with the decision making and you are researching the very thing that is interfering with your ability to enroll them. I mean, I think it creates a special problem that is different from the usual problem of obtaining all kinds of consent from people.

I hope you are not suggesting that we abandon the distinction.

DR. CASSELL: No, no, no. This is -- but as we begin to move out from that population, the people who were presented to us in testimony, for example, the really at-risk schizophrenic, for example, I do not want that abandoned for a moment. They are special.

MS. CHARO: Okay.

DR. CASSELL: But if they are special -- I think we get in danger by saying they are special and the others are okay. I mean they are special but how do we preserve that quality of their being special and research on them being done with difficulty and at the same time the others.

DR. MORENO: Well, I disagree that there is -- certainly you wanted this up front in the report. On page 11 there is a paragraph that I have framed as the Eric Cassell paragraph for which I need an Eric Cassell cite

actually. Why don't you jot that down for me? I would be happy at that point to insert any other language you thought was important on this but I do need a cite, Eric.

DR. CHILDRESS: Diane and then Laurie.

DR. SCOTT-JONES: The comment that I have -- I thought of it when Eric was talking so it may not be really related to what he said but I was thinking is that when we talk about consent we are talking about consent in the abstract and we are not talking about what the person is consenting to. For example, some aspects of the study may be easier to positive such as concrete details about what the person had experienced whereas more abstract elements of the research may not be easily comprehended by persons.

So it seems to me that sometimes we are talking about a person who has impairment as if that person is not capable of understanding anything and not keeping in mind that the person is going to be consenting to something and that others are going to be giving the information in a specific way. So I think we are losing the focus on the context in which persons give consent and we are thinking only about the individual outside of a context and outside of the others who are engaged in the process of giving consent.

DR. CHILDRESS: What would you like to see

changed or added?

DR. SCOTT-JONES: Well, I am just looking back to see if -- there is a section called individualizing consent and it is hard for me to find that because my pages are mixed up but there is a section here. Jonathan, maybe you can tell me where it is. Page 65? But I cannot find page 66 to see what is next. Okay.

DR. MORENO: Actually it is precisely this kind of concern that that section was designed to recognize so it would be very appropriate to add -- I mean, it would be no problem at all working out some more language on that.

DR. CHILDRESS: Diane, would you be willing to work with Jonathan on that standing and elaborating that as --

DR. SCOTT-JONES: Sure.

DR. CHILDRESS: -- that would be useful.

DR. SCOTT-JONES: Sure. And some aspects of Celia Fisher's paper might be relevant here because she talked about a relational perspective between the research participant and the researchers.

DR. CHILDRESS: And if you would use that as well in proposing changes here. Okay.

Laurie?

MS. FLYNN: I just wanted to underscore both

Eric and Diane's comments and just to add that I think it is important that we not lose sight of the fact, really two factors.

Number one, I think as Trish indicated most people even with most severe psychotic disorders are not decisionally impaired most of the time. If we assume that they are involved in any kind of treatment and even those who are not by nature of their illness are not psychotic and incapacitated most of the time. And I worry that we may have introduced a tone that can be stigmatizing to these individuals. It is important that we recognize that nearly everyone can make good informed decisions given an appropriate process in research settings. I am wanting to focus on what we need to do to make sure that that can occur so that the appropriate autonomy is retained by the individual.

The other question I have, and it may have been in here and I may have missed it, relates to how it is. It has already been discussed how we are going to structure the matrix around this and I think there are some problems with doing it by disease category because those categories are not as well described and well defined as we would like and because psychiatry is not yet an exact science. In my own daughter's case we have had four different diagnoses in twelve years and that is not

uncommon.

DR. CHILDRESS: Could I interrupt there?

MS. FLYNN: Yes.

DR. CHILDRESS: If I understood the discussion correctly we are moving towards using Trish's categories and then letting the disease categories --

MS. FLYNN: Yes. And I --

DR. CHILDRESS: -- is that okay?

MS. FLYNN: Yes. And I think that is a much better way to go.

I am also interested in how we -- if we have made any -- and it may be that we have not. I missed it in the organization here. Have we been able yet to describe the different categories of risk with any greater degree of specificity because that is a huge issue here and I think some of us who are trying to balance the need to strengthen informed consent and protection of decisionally impaired subjects need also to look at how we begin to describe what is greater than minimal risk, what is minimal risk because so many of these procedures come into question at just that point.

DR. MORENO: Let me note that there is a set of attempts to define by example that may help us a bit.

DR. CHILDRESS: Let me note that, and this will be when I go back to Trish, the comments for this

part are the structure, direction and tone of the report. So we will come back to risk with the next -- after we do this we are going to talk about decisional impairment and incapacity in informed consent as one big set of topics and then risks and benefits, and then procedures such as advanced directives and then recommendations.

MS. FLYNN: Jim, then just if I can make a final comment. Again, as I did last time, I want to thank you for your continuing and evolving sensitivity to the role of families and caregivers, which I think is an important addition that you have made in each of the drafts of the paper and I think it really is an important piece particularly for some of these individuals who have fluctuating capacity over long periods of time.

DR. CHILDRESS: Okay. Trish, any last comments on overall structure, direction and tone? Remember we will come to the particulars later.

DR. BACKLAR: You knew exactly where I was going. All right. Right, I will hold back. One of the references that I think that you might want to look at in terms of what Laurie was saying and in a particular group of people who much of the time do have capacity for decision making as Appelbaum has some good papers and I will be glad to give you the references on that. So that people reading this will understand that this particular

population does and can often have capacity to make some decisions in some ways as well as the general population.

DR. CHILDRESS: Any other comments on this first topic?

DR. BACKLAR: No. I think it is going very well.

DR. CHILDRESS: Laurie?

MS. FLYNN: No.

DR. CHILDRESS: Okay. Alta, and Diane, and then I want to get Alex's comments on the overall structure.

MS. CHARO: All right. I think this is structured. One of the things that happens in this report because it happens throughout the regulatory approaches that are proposed is a very reductionist way of approaching things in which we identify one or two key variables like risk and population. I found myself wondering at a certain point whether we should be considering the synergistic effects of some of these factors and cutting things that way.

So, for example, when recommendations are made about the possibility of consent monitors, is it appropriate to think about them when you have got a population of people with decisional impairments who are institutionalized because that is a special

synergistically vulnerable population or where it is the treating physician who is the PI and that it might be a different way of thinking about what triggers different kinds of protections rather than the simple population versus risk matrix that we are used to using.

I do not know if that is structure or something else but I did find myself thinking this might be --

MS. FLYNN: That is a useful --

MS. CHARO: -- a place where -- in fact, Diane might call it a more contextualized approach.

DR. CHILDRESS: I think, Diane --

DR. SCOTT-JONES: I just had a couple of comments about overall structure and tone but, Jim, I did not know if you were wanting to get through all the people that you assigned to talk about that first or do you want our comments --

DR. CHILDRESS: I think it would be useful actually to get Alex's comments. I think Laurie and Trish have finished their general comments --

DR. SCOTT-JONES: Okay. And then I will --

DR. CHILDRESS: -- but Alex's, I think, will --

DR. SCOTT-JONES: -- my two.

DR. CHILDRESS: Okay. And just make sure --

DR. SCOTT-JONES: Okay.

DR. CHILDRESS: Alex?

MR. CAPRON: Well, I echo the previous comments that the draft is moving along well. In terms of structure and tone the problem that I have in part came into focus with Eric's suggestion for which he retreated a little or clarified in a way because this is something that comes up in the first chapter here very much and that was you were suggesting, Eric, that we tie the discussion here into a broader reexamination of the issue in a sense and the inability that people who are sick, and patients have to give an informed and voluntary consent because of their circumstances.

Likewise already in the discussion besides the Cassell paragraph there are discussions of things like the therapeutic misconception that plays into that, too, but it is sort of a separate topic. Even if you were quite capable are you being implicitly misled by the way things are presented?

I have found some of the discussion hard to follow but beyond that I was concerned that it was in some ways a diversion from what it seems to me this report ought in its opening pages to make very clear, which it does not really do. And that is why this report? And it is fine for us to signal that the commission will be

looking at broader issues and I assume that part of our process in the future, Jim, that we can consider is how -- to what extent should we more generally revisit certain basic assumptions.

We said more than a year ago that some of the ideas in the Belmont Report might need to be reexamined if not as principles at least as principles applied to the field. I think that is fine for us to drop a footnote as it were to say this is merely a particularly acute problem as the way Alta answered you and I agree entirely with her answer that when you are dealing with an illness, which itself is an impairment of the capacity and that is what you are researching about, it complicates things substantially but that we recognize that it is not a unique phenomenon. It is simply a particularly acute example.

But what is missing to me here are -- is a clear statement of what our task is, which to me as of now until we revise the whole structure supposedly if we ever do that, is how to incorporate the cognitively impaired into the framework of protection of human research subjects. That is what I thought we were all about and that is something that the national commission tried to do and in its recommendations in this one area did not succeed.

So I think we need right at the beginning to say why that is. Some of the difficulties seem to be inherent difficulties. The ways in which the ability to deal with personal contemporaneous consent are interfered with. They may be interfered with very temporarily and so you can look to another time period. They may be substantially interfered with. The interference may be very peculiar to the ability to assess risk to one's self. Whatever it is, but there are difficulties here. That is why we use the word "impaired."

Secondly, the settings for some of the research raise the issue particularly acutely for people who are in psychiatric facilities particularly as long-term patients. Their role creates a special vulnerability that is beyond that for people who have other dread diseases.

Third, we have to recognize the marginalized nature of this field and the people who suffer from these illnesses, which again makes them particularly vulnerable and it makes them also vulnerable to the fact that they have limited -- often have limited access to other resources. Their insurance may be inadequate. They may be in a condition because their medical condition interferes with their ability to have a livelihood which takes them outside of an insurance mechanism and they are

just generally regarded by people as having the kinds of illnesses that make them difficult to be with, that doctors feel frustrated, the armamentarium of responses may be inadequate or they may be resistant to using what is there. All of these are problems.

Fourth, there is the nature of the illnesses themselves and there is a reference in here, but you can almost miss it, to the sense that unlike many other illnesses -- although I am always worried about making anything too categorical -- but unlike many other illnesses a difficulty has been the absence of good animal models for many of these illnesses so that there is this kind of weak forward to human testing at a stage when one might otherwise in another illness be trying to do work at the animal level. I do not know the extent of that but you make amendments to it.

And then there is an additional factor, which seems to me less intrinsic but nevertheless very pronounced, and I get this more -- the more I read about the research in this field. I have a sense of a separate research subculture which has not been as sufficiently affected by the last twenty-five years of examination of these issues. Maybe for all the inherent reasons they apparently explain it and it is not a desire to be on the attack against it. It is simply a recognition as to a

need to especially address and to respond to the concerns that may have led people to behave as a separate subculture.

But as several people have said in exchanges of e-mail it would be impossible to imagine people with the severity of the diseases that some of the things we have seen being put into frank relapse of their cancer or other life-threatening conditions -- these are life-threatening conditions for some people -- in order simply to see what happens. It is at that level equivalent to a Tuskegee study it seems to me and is to say there it was the observation. Let's watch what happens in the natural course of this illness without treatment. It seems to me that part of the outrage over there had to do with that.

So I think these factors have got to be front and center and I do not want to wade through a discussion of the therapeutic misconception and other things until I know why is this.

The second thing along --

DR. CHILDRESS: Let's stop on the first one just a moment.

MR. CAPRON: Yes.

DR. CHILDRESS: Now, I take it in your summary you were included some things that are already here as if you were --

MR. CAPRON: It is --

DR. CHILDRESS: -- listing because there --

MR. CAPRON: -- organization. It is not that the materials are not to be found somewhere in the report --

DR. CHILDRESS: But then there are some things, including the institutional kind of research subculture here --

MR. CAPRON: Yes.

DR. CHILDRESS: -- that do not appear.

MR. CAPRON: Yes.

DR. CHILDRESS: And I take it that the articles you were directing us towards and the kind of research you wanted might go get at some of that.

MR. CAPRON: Yes.

DR. CHILDRESS: Is that correct?

MR. CAPRON: Right. And to elaborate on the point you were just getting to, I think we need to bring home to the general reader some of the things that we have seen by way of these research studies, Jonathan. That is to say any -- a person just coming to this cold ought to have described to them some of the published studies and the way that they were done. Again it is not a matter of singling out Dr. Jones and saying whatever. It is a matter of saying that respected researchers in this field

--

DR. CASSELL: A la Beecher.

MR. CAPRON: Yes, a la Beecher, exactly.

DR. CASSELL: Yes.

DR. CHILDRESS: A la Beecher. The names of the researchers were not important. I mean, he was even more protective of which studies he was dealing with and shared with the journal editors the citations to -- these are all in the New England Journal , of course. The articles that he was referring to. But just to make clear the problematic nature of the field that these kinds of things have happened.

And I would also have right up there in front a brief statement of the regulatory -- which is then elaborated in the second chapter, I guess -- the regulatory efforts. In other words, we are not the first group of people to come to the field. And then I am talking about something of a paragraph length at this point but those recommendations did not go forward. This produced the following sort of ironic situation that on the one hand some people feel they can go ahead with research with no special protections because the code does not provide for special protections. Other people feel that their research efforts -- they cannot go ahead with the research because the framework for special protections

does not exist.

And at the very least because of the kinds of issues that I have just mentioned, these inherent and maybe extrinsic special factors here, this is a field that cries out for a careful regulatory response that will bring this population finally into the umbrella of the protections. Not getting yet into the question of whether those protections themselves need to be rethought and tinkered with or totally refined or something. But we have these protections, it is all we have now, yet this group does not get the attention.

I want to be able to pick up this report and in the first ten pages know why I am reading it. Okay. Why this is a concern. Why action must be taken. And I think we all feel that that is the case and it is a matter of focusing it more sharply and putting some of the stuff, Jonathan, that is in the first few pages now further back or --

DR. MORENO: The first chapter keeps turning into a subsequent chapter but that is fine with me. But I just want to observe from the drafter's chair that the charge that the subcommittee had in mind last time was a sort of generic, general educational, almost text-like textbook-like document. This is a more reformist, which is fine with me. This is out of a more reformist approach

which is consistent with other things that Alex has said before. I just need to know if everybody wants to buy into this.

DR. CHILDRESS: Alex, do you mind, before you go to your second point, your first important set of comments spoke to several hands so could we sort of address the issues surrounding the first one before we turn --

MR. CAPRON: Yes.

DR. CHILDRESS: Okay. I have Diane, Eric and Trish. Alta, you are down -- you are sort of out of my line of vision so you will have to be -- you will have to --

DR. CASSELL: Move to the other side of the table.

(Laughter.)

DR. SCOTT-JONES: Okay. I have a couple of comments about overall tone and structure and these are directly related to what Alex has just said. The first has to do with the statement of purpose and the placement of this statement of purpose in the chapter and then the second has to do with the role of researchers and researchers' understanding of their role.

For the first one, if you look on the first page of chapter one in the first paragraph it is the

statement of the purpose of this report. I think that statement needs to be at that point considerably beefed up before moving on to examples which come in the next paragraph and you can look forward to page three, the end of the second full paragraph, there is another statement about what the report's purpose is and it is a little bit different from the purpose stated at the end of paragraph one.

The paragraph one purpose statement would lead a reader to believe that perhaps we are questioning whether research should go forward and I think that statement will cause researchers to react in horror because they will immediately think that commission is trying to halt research and halting research is bad.

So I think that tone needs to be taken out of there or elaborated immediately at this point with a richer description of what the report is going to be about so other places throughout chapter one where there is an elaboration of the purpose. Whether it is as Alex described it or not, I think it needs to come here so that will be clear to a reader from the very beginning what the purpose of the report is.

I think it should not be set up this way because I think it is set up in a way to polarize this more than I think reflects most people's thinking.

Then the second point that I have has to do with the role of researchers as it is presented in this first chapter and what I think researchers' understanding of their role is. On page four, the first full paragraph, refers to a subject of research being engaged in a form of public service but are we then saying that researchers see themselves also as engaged in a form of public service because they are engaged in the same research enterprise. If you look at page ten there is a much more negative view of researchers' role in research and that is that they are trying to make money and advance their careers.

So there is not a consistent presentation of what we understand to be the role of researchers and of researchers' understanding of their own role. I think we should be clearer about that. We cannot at one point say that research is a form of public service for the persons who participate and then a few pages later say that for the researchers themselves this is a source of advancement financially and advancement professionally.

DR. MORENO: Can I just say that this was a statement that was made at the last meeting. Mainly that it should be -- it is important to say that people who participate in research are doing public service. It is also important to recognize the external considerations that drive researchers. So if you want to change that I

also would need to get some --

DR. CHILDRESS: It is possible to have a view about research's role in society as a whole, the functions that these different individuals, including research subjects and researchers play, and distinguish the motivations of all those individuals from what we said about the other. That is I do not think they are incapable but we need to be very clear about which level is being addressed in point because the research subjects also have a variety of motives for taking part in what is a public service but their motivations might be relief of boredom or whatever.

DR. SCOTT-JONES: If you ask researchers themselves what they think about what they are doing they may bring up academic freedom, that I study what I want to study, and that is still another perspective. I will just feel better if there are --

DR. CASSELL: Aerosmith rides again.

DR. DUMAS: But what is the relevance of that? Why is it important to comment on that in this report?

DR. CHILDRESS: I guess, Diane was making the observation that insofar as we do make comments along the way we need to at least --

DR. SCOTT-JONES: Right. And I --

DR. CHILDRESS: -- we need at least to be

clear and consistent in what we are saying about --

DR. SCOTT-JONES: Right. We need to have a clearer view that we agree on about what the research enterprise is for researchers and for those researchers on understanding of their role because they are going to be reading this document, hopefully, and I think we have to be crystal clear about that and I do not think we can at one point say, "Well, people should participate in research for the public good," and at the same time turn around and say, "Well, researchers are in this because they are making money and advancing their careers."

DR. CHILDRESS: But then distinguish the public good aspect of the role as -- distinguish from the motives individuals might have for entering that role.

MR. CAPRON: But I think Diane could fairly be saying that one of their motives might be scientific curiosity, the desire to add to knowledge, as well as the fame and material benefits they would get from that.

DR. CHILDRESS: Right.

MR. CAPRON: They are not going to get either the fame and the material benefits if they do not add something to knowledge.

DR. CHILDRESS: Right. And I think the point is well taken that those modifications can and should be made.

MR. CAPRON: Yes.

DR. CHILDRESS: Okay. I remind you I want to get Alex's other points and I have Eric, Trish and Laurie, who are basically tagging in on Alex's bigger point about why this report, et cetera. Okay.

DR. CASSELL: First of all, I agree with you, Alex. I think there is something special about the group and that should be made absolutely clear but for my own philosophical perspective of it I think that what the first commission did was, in part, recognize that sick people are persons and that that was happening at that time in the culture. It was not just the commission but it was going on in the culture. In the subsequent time we have seen women in public and most recently persons with disabilities become persons, fully accepted persons, but not the psychiatrically sick yet.

I think that the way that the very psychiatrically sick are treated and receive -- and you just produced two papers, right -- seeming abandoned of those principles which are now present as you have pointed out. And in cancer you have to explain that to someone. You cannot do it by just saying there are bad guys and people who do this thing. But somehow their relationship to the subject is different and I think that the problem is that the subject is still a nonperson in this culture.

I think that you are absolutely right. It should be made clear. It should stand out in front for everybody to know. That is on the one hand. But on the other hand what issues we raised before and my own particular concerns are still present. I think that the first commission ducked the problem, it incubated the sick persons and, therefore, gave them the ability to consent for themselves when, in fact, they do not have that -- in fact, maybe we should, so we may be able or may not, but we may be able to start picking up that challenge of how to solve the problem of persons whose capacity to make decisions is not entirely like that entirely.

MR. CAPRON: Are you agreeing we would signal that is a bigger project that we are at work on? We will not have to resolve that for this report.

DR. CASSELL: I do not think we have to resolve it. I think we have to say that it has to be resolved at this time. I mean, the commission as a whole may say this and we do have to resolve it but I do agree with you that we are here about this group because they are special and that we should not dilute that. On the other hand, I would hate to see us as a commission give up on the other problem.

MS. CHARO: Can I just ask for a point of clarification from Eric?

DR. CASSELL: Yes.

MS. CHARO: Jim?

DR. CHILDRESS: Yes.

MS. CHARO: I am trying to -- I mean, I was -- I am intrigued by this notion that there is a special subculture in the research world and I do not know for myself whether it is true or not but are you talking about the problem with empathy when you are talking about the nonperson's thing that the researchers cannot empathize enough with these subjects because the nature of the illness is one that presents empathy and that, therefore, there is just an obstacle to considering things from their point of view in a way that is necessary to take these things seriously?

I mean, I am trying to understand the meaning of saying that they are treated as nonpersons in a way that I can understand. It is the phrase of something kind of academic.

DR. CASSELL: Can I address that briefly?

DR. CHILDRESS: Briefly.

DR. CASSELL: Yes. I could show you medical people who are medically sick where you would have great difficulty with empathy. They stink. I mean, literally smell and look so bad that you would have trouble.

MS. CHARO: Okay.

DR. CASSELL: But your heart would be rendered by the fact that somebody should be in that condition. People who are not nonpersons like people who are never sick used to be when I first went into practice, you could be kind, obedient, cheerful, thrifty, brave until you were wonderful but they are not like me and you. They are different. And that is, in fact, the way the psychiatric ill are treated. They are different. They are not just sick. They are different. And it is the erasure of that difference that comes in part we are addressing.

DR. CHILDRESS: I have Trish and Laurie for brief comments in relation to Alex's first point.

MS. BACKLAR: I agree with Alex completely that we have to set up saying why we are doing this and I think one of the problems that keeps escaping us is that it is not simply the consent issue. It is the progress of the research and what happens to people with this disease, these kinds of diseases, is that they can lose their capacity to care for themselves or to make decisions. So there is a whole group of people who may enter into the research. I know you all know this but I want to make it very clear why this becomes so complicated. It is not simply just agreeing to go into the research. It is how we deal with it as it goes along.

The other thing is that I fear that we as a

commission, people are looking puzzled when Alex is referring to these challenge studies, and that maybe you did not get to read them, and I also suggested to Jim, and I do not think this came out, three other studies that had been given to us in earlier -- at another one of our meetings and had pointed out these kinds of studies -- we do not do this with people who have AIDS. We do not promote their illness in order to study it. I think it is very important that we address that in this report and in our discussion.

DR. MORENO: Okay. Can I just -- again from the draftperson's point of view the challenge -- if the challenge studies are the only ones that the subcommittee has trouble with and you are talking about specific population of disease, and I can imagine that some people will say, "Gee, that does not affect the kind of work I do." So we need to be careful about that.

MR. CAPRON: Well, I think we should have a broad description of things other than just challenge studies.

MS. BACKLAR: Yes. One other thing in terms of what Diane was saying, I also think that one cannot give up addressing the fact that as David Rothman has said, the gilded age of research and the research industrial complex does play some part in here, both

private and federally funded, and the pharmaceuticals and so on and so forth. So there is money in here and money plays a big thing even in terms of subjects, which you did not address. This is getting a little diffuse.

DR. CHILDRESS: Okay. Laurie?

MS. FLYNN: I guess I want to make two comments that will sort of sound like an opposition to each other. This is a painful discussion to be part of as someone who is in touch with these illnesses and individuals as I am and I think we need to emphasize the otherness of this population. The culture, our society, reflected in many, many ways continues to keep these folks at a distance and to see them as inherently different and in some ways less human than we are.

DR. CASSELL: That is right.

MS. FLYNN: And we do need to say that. At the same time I am not comfortable, and I want to be clear that I am really not comfortable with the tone that comes through in many of these discussions that tends to isolate that particular societal response to the research community. The research community is in need of more guidance and we need to strengthen the protections.

But we are sitting today looking backwards at research studies and trying to interpret studies that are going on in an arena where until quite recently there was

very little research where the stigma that attaches to the disorders attached to the research too. I would be leery of our making judgments as nonscientists about the perceived value of individual studies.

I, for one, am uncomfortable, for example, with so-called relapse studies. But I also know that many of these studies were done in a time in an era, and even today there persists a strong belief in some quarters that mental illnesses are really not biologically based, that medications are themselves more toxic than illnesses, that these illnesses are somehow as yet not well enough catalogued to be able to be effectively diagnosed and treated, and in some of these instances the provoking of relapse was an effort to try to determine what, if any, are the biologically underpinnings of some of the symptomatology that we see. Some of it can be quite distressing moving from disorientation all the way out to aggression.

So it is easy for us today to make some judgments about the hypotheses that were being tested and to do it from the framework of a much more sophisticated understanding of the brain mechanisms but we must remember this has only been achieved in the very recent past and I am much more comfortable emphasizing the otherness of this population than I am taking lines of research to task.

I think we get into deep water when we start trying to intuit the motivations, either scientifically or personally, for any group in society and certainly given what I know of the lack of reward for research in schizophrenia for so many years, the lack of prestige, the lack of career advancement, I fear that we may literally tar the reputations of some individuals who have been singularly helpful in bringing this population forward into a much safer and much more sophisticated research environment.

DR. CHILDRESS: And the last point on Alex's first point and then we will return to Alex, Diane.

DR. SCOTT-JONES: I would like to make a point related to some of the ones that Eric and Laurie have made about being respectful of persons we are talking about in this particular document. I think it comes through in the language that we use to describe them. So I am pleased to see that most of the time we say persons with decisional impairments instead of saying the decisionally impaired because we are labeling the whole person when we use that latter phrase. So I would suggest that throughout we try to get rid of the language that labels persons in that way and always even though it may be a little bit more awkward and maybe not always as elegant to say persons with decisional impairment or something that names them as

persons and not just by that category.

DR. CHILDRESS: Thanks. Alex?

MR. CAPRON: The other two comments that I have are small about tone. One has to do with the use of the first person plural and I do not like "us". When you are not actually even referring to the commission it is "us." Somehow there is vague "us." If it is other research subjects we say other research subjects. If it is all Americans when we feel we can confidently say all Americans. Also I think a lot of the times the phrase "the commission believes" or something is unnecessary addition. Obviously this report is our beliefs and conclusions and findings and so forth. I just -- it is just filler.

DR. MORENO: Rhetorical filler.

MR. CAPRON: Rhetorical filler.

The other point loops back to something that Laurie was just saying. Some of the times the concerns that arise here are expressed as the concerns of this group of patients and their families. And there may be times that the concerns are that narrowly focused. I have a sense that many of those concerns are shared by the researchers, that is to say the concern that on the one hand we do not want to have injury and on the other hand we want to find some answers to these terrible puzzles and

these awfully burdensome diseases. They are shared by the members of this commission and probably by most people.

So while it seems to me useful, if the observation is that a particular concern is surprisingly found even among the families, then to put it that way that it is even -- and even has been articulated to the commission by family members, then fine. But otherwise I do not think we should -- to me, again to use your concern, it almost marginalizes that this is something, this is a concern of the subgroup. I think it is a broad concern.

But let me make clear about my comment about the research culture, which was not as broad as the comment that Eric added to it. I was not looking at the motivations as much here. I was descriptively saying that in part because the regulations have not specifically addressed the problems that people trying to conduct research or subjects trying to be subjects as it were in this research phase because they have not said, "Yes, there are some special concerns and here is how you deal with them," it may be for that reason or whatever, it just seems as though -- or maybe because their academic colleagues marginalize them, I do not know, whatever reasons, but it is as though there really is a group that has not had the same attention to the kinds of things that

45 CFR -- whatever it is now, it is not 45 CFR, whatever it is -- is it still 45 CFR? I thought it was 21 or something. Anyway wherever --

DR. MORENO: That is FDA.

MR. CAPRON: Okay. They have not had apparently as much attention to these. I mean, maybe the research community -- this research community has not gone through as many of the educational seminars. I do not know what it is but you do just get a sense. And the reason for pointing to any of these is not to say, as I said before --

DR. CASSELL: You do just get a sense --

MR. CAPRON: You do just get a sense that it is a separate community. So the reason for pointing to it is to show that research is carried on which does not seem to have attended to the obvious concerns that arise, not to say the challenge studies, anybody who ever did a challenge study is bad and not to say that there were not questions that they had addressed. Not in other words to pass on the scientific reasons for the research or even the scientific benefits the research had but just to say that things have been done and are being done in publications in 1997, which is what I shared with you all, which indicate that a problem exists that is not at least on the surface adequately attended to by the researcher.

I mean I would expect that if they had adequately attended to it their methods section in describing how they recruited the subjects and how the IRB dealt with these issues would have gotten big attention because it just -- to anyone reading it with that eye it leaks out of the report and yet it gets no attention and no attention at such a level that you have to think that they did not think it was a problem.

I have a sense, as Trish said a moment ago, someone doing AIDS research would have said, "I have a problem here. I have got to figure out how to deal with that problem and then I have got to tell people that I saw it as a problem and this is how I dealt with it because anybody looking at my research would otherwise say --"

So it is not a matter of being these people. It is sort of saying that we are dealing with another factor that is a reason why we have to give special attention here because there seems to have been a research subculture that does not seem to have been brought into this.

MS. FLYNN: If I can just comment. You may be correct but I am not persuaded that is the case. I think there is a need to strengthen the protection for this group because of the cognitive impairments that they bring to the research enterprise. I am much less certain that

there is some particular lack on the part of the research community as a whole and I am concerned that we would seem to give the tone that this group somehow as a subgroup of the research community has brought less than their best effort to this arena or has been less than appropriately sensitive. They have, in fact, worked within a framework they have been given. There have been those who I am sure have reached the ethical barriers that have been in place but I am concerned that there is this kind of broad brush characterization that I do not think is brought out by the reality.

We heard in this commission on the occasions that we have had comments from a very small number of highly vocal individuals bringing situations and conditions that deservedly got attention and they are deservedly concerning. But I would posture to you that they are not representative of the large number of experiences of the large number of individuals with cognitive impairments at least in the mental illness arena who participate in the research. At least we have no evidence that they are.

So that while I think we ought to be very clear that this group needs additional protections and while we ought to be calling for more attention to ethical principles on the part of the investigators, my concern

goes to making them sort of the judgment about a subculture that I am not certain is supported and I am concerned that we not say that.

DR. CHILDRESS: There are two responses and then Alex wants to get in. But let me just say that maybe it is possible to point out the need for the protections as you suggested without necessarily offering a full explanation which is what the --

MS. FLYNN: I mean, the fact that these folks are excluded from --

DR. CHILDRESS: -- subculture tries to do.

MS. FLYNN: -- the Common Rule is enough. They are excluded currently.

DR. CHILDRESS: But without --

MR. CAPRON: Laurie, I do disagree. I do not want to base this, as disturbing as the things we have heard here, on what is anecdote to everyone. I want to look at the literature and that is why I started bringing these studies forward. I want our research staff to search the literature. I want them to look at these -- at research on psychiatric illnesses and see whether the studies which we have begun to turn up are indicative that there is something that needs to be addressed.

I mean, if I am sitting as an American citizen or as a member of Congress or whatever being asked, "Why

should you have special regulations in this area," I do not want to base it on the fact that someone says, "I was at NIMH at the clinical center and I was given a stack of consent forms and asked to sign one after another." I cannot imagine a patient in the hospital for diabetes asked if he can sign 20 or 30 consent forms at once and being told that is standard operating procedure. I cannot imagine an IRB would allow that. Apparently it happened there but I want to gloat on that.

I want to look and see research studies in which people were given challenge doses of chemicals that brought on psychiatric -- that brought on psychotic symptoms, that brought on cognitive impairment, and the study does not address at all such questions as what long term effects are there, how are those being monitored. There is not attention to that. I cannot imagine that in another -- I mean, just go on and on and on. And this is not anecdotal. This is the published literature.

DR. CHILDRESS: That is the question today and we are trying to address. The question being whether we -- how far we need to go in terms of an explanation. I think that the --

DR. DUMAS: I think that is one of the critical issues here. I think we are trying to do too much with this one report. I think we are getting into

too much detail and I think we need to get kind of a broad outline, a framework, for what it is we really want to convey and how to attend to that. And my concern is that we are losing -- in the details we lose the principle reason and purpose for our concerns about this.

Now, for example, we are concerned about the protection of human subjects in research and I see the mentally ill or the decisionally impaired -- I see the decisionally impaired as being a broader category than just people who have mental illness or disease. But I believe that the people who have mental illnesses provide a dramatic example of the kinds of difficulties and problems that one confronts in this area and I think it should be treated that way as an example of problems in securing informed consent when there are certain impairments in decision making.

I think our guidance -- there should be guidance that will enable the researcher and the IRB's, the people who are participating to the extent that they can, and those people who are caring for them to make certain decisions about whether or not they are able to participate and at what points. And I think we get lost in the details of this report and I would like to suggest that we try to filter out those things that may be important and interesting to consider but not specifically

relevant to those basic purposes.

DR. MORENO: Jim, I wonder if I might not suggest a way out of this but I am sure it will not work. The Radiation Advisory Committee already went through a procedure very much like the one that Alex described and it functioned you might say as kind of a post-hoc IRB and it found reason for concern, I think was the kind of language that was used, about a number of studies that have gotten through a couple of IRB's, both NIH and local boards. Some of those studies involved, for example, substance abuse studies. I think that the advisory committee can cite the Radiation Advisory Committee's work in general, sign on to that and also indicate that there are some specific kinds of studies in these areas that concern us in the same spirit as that of the Radiation Advisory Committee.

DR. CHILDRESS: Alex? And then I have got Diane and then Bill Freeman.

MR. CAPRON: I am happy to see an attempt along the lines that Jonathan just described. I think that we are dealing with something that is more akin to what Henry Beecher faced. I do not think there would have been in the years after 1966 when that article was published the receptivity in the scientific community, the medical community, or the general public, people here at

NIH for that matter, to the notion that there really was need for attention to this if it had not been made clear that respected researchers at respected -- publishing in a respected journal had example after example of -- what was the phrase that you just used? It is a questionable --

DR. MORENO: Reason to --

MR. CAPRON: The questionable concern.

DR. MORENO: -- that there are reasons for concern in the current system.

MR. CAPRON: There are reasons for concern that the ethical principles are not being applied to a category of research and again it simply says this is something to take seriously. This is not a few people -- unhappy people complaining because something bad happened to them. That happens in every field, et cetera, et cetera. This is an area that needs attention. That is all I am trying to say. There are reasons for concern. So I would be happy to see you try to bring these examples in and it should not just be the challenge studies. I quite agree. Those are dramatic examples but I am sure we should look elsewhere. It is not a matter of then saying this is X percentage. We know this to be X percentage of all studies in the field. Either 100 percent or one percent. It is just an example that there are reasons for concern.

DR. CHILDRESS: And as has already been noted not only do we have the expressions of concern on the part of the research subjects and families but also on the part of researchers who in a number of the articles supports an indication of the need of clarification. So at least there are several reasons --

MR. CAPRON: Yes.

DR. CHILDRESS: -- and that perhaps could be elaborated as well.

Okay. I am going to take a -- let's see -- Diane and then Bill Freeman comment here and then we will see if Alex has any more general comments.

MR. CAPRON: I do not.

DR. CHILDRESS: Okay.

DR. SCOTT-JONES: I have a comment about what I thought Alex was saying earlier. Alex, it seemed like you were raising a general issue of whether researchers exist in sort of a separate subculture with a different perhaps set of values and standards for their own behavior and I do not know if we need to comment on that in our document but I believe that what you are suggesting is, in fact, true to some extent among researchers because a researcher's goal is generalizable knowledge and it is to the researcher's interest in pursuing that goal to enroll everyone in a study who is eligible for it.

But if on the other hand we have informed voluntary participation in informed consent that means that some subset of those people ought to be able to decline to participate and that is good for them. In the researcher's world that is bad when any one person refuses. So there is inherently a separateness of the researcher's goal from the goals of persons who are considering whether to participate.

I think we have to recognize that and not pretend that does not exist. For many researchers the attention that is given to ethics represents an obstacle to their conducting their research on an everyday basis and they dislike it enormously.

Although I agree with what Laurie is suggesting that people are probably well intentioned but in the real research world on an everyday basis many people dislike enormously the fact that they have to go through this process and I suppose we should recognize that but somehow I am not quite sure how we do that. But it certainly exists.

DR. CHILDRESS: I take it Alex though was also making a further claim that within this subset of researchers --

DR. SCOTT-JONES: It is especially bad.

DR. CHILDRESS: -- it is -- right. So, you

know, that is probably the issue.

MR. CAPRON: I think even -- I mean, I actually do not think that Laurie and I are that far apart. I mean her very comment that this group of researchers has faced obstacles themselves and has not been as appreciated by their scientific colleagues -- maybe part of the difficulty is the difficulty of conducting research in this field as well as the frustrations of understanding the mechanisms of the diseases involved have made it harder to have the kinds of concrete findings. Now that can lead several different ways.

It can mean that you are a separate culture to a certain extent and it can also mean that your drive to break through that barrier is all this -- I mean, I do not know. I suspect that some of the other things that were criticized -- and Charlie McCarthy's paper which we are talking about later gives us a couple of examples of people working on the far edges of somatic biomedical research, gene therapy and bone marrow transplantation, and some of the people there -- a couple of examples from UCLA -- were of people who stepped over that line. I am sure part of that was that drive to break through and so forth. Sometimes it leads people to do bad things.

But their culture that they were in recognized

that they were stepping over the line. I get the sense that this is a group of people who when looking at each other's work do not see that they have stepped over the line.

MS. BACKLAR: And part of that is because of the population that they are dealing with and that old time long-term stigma that these people are not like us. That still pertains.

DR. CHILDRESS: All right. I think there are several directions that have come out. Not all of them are compatible with each other. We will have try to some drafts and maybe even a couple of different versions of structuring this material and then see where we go.

Bill gets the last comment.

DR. FREEMAN: I am going to try a compatibility thing. It seems to me -- I come at this as an IRB'er. These articles -- this research was reviewed by IRB's. It was also reviewed by grant funding people. It is not just researchers or a bad subgroup of researchers that is the problem. So I think, what Laurie is saying, to focus on people who are doing it -- in fact, there is only one group of people who are involved in the chain of approving this project is incorrect. In fact, we do not know what IRB's and researchers have done that have not done this research. It was proposed to look at this

and they did something different that was ethically acceptable.

The problem it seems to me is that we, the society, have not had a consensus about what is the meaning of our ethical standards of research in this subset of research, not researchers. There has not been a national commission that has established our consensus. There are not regulations derived from that consensus. In the absence of the consensus do not be surprised if we have what we now consider to be unethical research being proposed and done by ethical researchers and ethical IRB'ers and ethical grant funding agencies. I think maybe focusing on society is the way to look at it.

MS. FLYNN: Thank you.

MR. CAPRON: Let me if I may just add one analogy to a different field that we have dealt with in our cloning report where it does not touch the sensitivities of people around the table as much. We had no problem in saying that one of the reasons why we thought the so-called private sector needed to be addressed was that the subset of people working on the infertility field were apparently willing to do things which a lot of others looking on in society thought were stepping over the line and that if cloning was the kind of thing that they could do technically this would not be a

group that had shown itself as subjects to self-regulation as for example people doing heart transplants or something. An equally cutting edge field.

So that there are times when we have recognized that within the broader group of biomedical acts there may be a subgroup that seems to have its own subculture which sometimes raises questions for us and we did not have any problems, I think, with that and the implications that we needed to address.

DR. CHILDRESS: Harold, and let me also then just see if there are any final comments on the broad topic, and I think a number of important issues have come out regarding the overall structure and direction and tone of the report, and I think that we can work out some of these that will be much further along in the report.

DR. SHAPIRO: Again, I think you are still in the area of overall structure and motivation. I very much associated myself with Alex's comments. This is a very important report. More important than any other report we have written so far and involves what we will do in the future but it is really important in an important area and so we have to be cognizant of that.

I also think it is good to have what I call a parsimonious principle regarding motivation. That is we ought to attribute motivations only when it is necessary.

Otherwise we just ought to be silent on motivations and in all the issues that have come up today we really -- I would not say all, most of them -- we could use the parsimonious principle because there are very strong compelling reasons to reach the same conclusion without worrying about whether someone worries about money or worries about professional advancement or just concerned about disease or whatever. I just think that is helpful as we go through this.

And in some areas -- and this is a small point really because it only comes up one or two times, if we -- some areas are settled by data, information. And when that is settled we ought to have the information or we ought not to opine on it. So, for example, let me take a very small, not very direct example, a not very important example. That is we say that private funding, meaning by this case corporate funding, has added a new dimension to this which is important somewhere. I have forgotten exactly where it is.

Well, maybe that is true and maybe it is not true but it is set-able by knowing, you know, what proportion of this now compared to ten years ago is here. And so in those cases where we find that in the report where data settles the issue we ought to get the data together and it is the same point Alex made in

relationship to his review of the literature on another issue all together.

MR. CAPRON: Would you accept one comment on that? I agree with everything you have said and I certainly do not think we want to attribute motivation unnecessarily.

There is a difference between attributing motivation and to follow up on your comment about additional corporate funding in the area.

If the proportion between basic research funding from NIH and corporate funding shifts and if that corporate funding is mostly on the development of drugs and if we also know that people in those corporate run studies are paid substantial amounts of money for recruiting subjects, et cetera, et cetera, without talking about their motivations or however you want to word it, we should have a risk factor which makes --

DR. SHAPIRO: Absolutely.

MR. CAPRON: Okay.

DR. SHAPIRO: Absolutely.

MR. CAPRON: Then we are in agreement.

DR. SHAPIRO: Absolutely right. That is exactly right. I agree.

DR. CHILDRESS: Okay. Any last comment on the overall structure and direction we are going?

DR. CASSELL: We have gone over a good deal of ground.

MR. CAPRON: I know the chairman is worried we are not --

DR. CHILDRESS: No, I actually think that --

DR. DUMAS: I thought that the first chapter was quite an improvement and I thought that despite the finetuning that is going on now that the second draft really took into consideration a lot of concerns that we had earlier and we have made -- you know, we have come a long way.

RESEARCH WITH DECISIONALLY IMPAIRED SUBJECTS

DR. CHILDRESS: Okay. We are going to turn then to decisional impairment, incapacity and informed consent. And in thinking about each of the areas we are going to look at now, that area, risk and benefits, and procedures, we might also keep in mind the tentative recommendations that have been formulated and think about not only the discussion that builds up the recommendations and we also talked earlier about those in which we need to develop that build up even more, but also the kinds of recommendations that are tentatively proposed. So as you are working on this area if that is possible to keep in mind then do so.

I have Arturo first and then Diane, and then

Eric on the decisional impairment, incapacity and informed consent. The discussion that runs throughout the report.

DR. SCOTT-JONES: Jim, could I ask a question before we begin that? So then are we pleased with the placement of the historical chapter?

DR. CHILDRESS: That is actually a good structural question. Did you have a comment about the placement of the historical chapter?

DR. SCOTT-JONES: We are skipping it in our discussion. Are we pleased with --

DR. CHILDRESS: Well, these are not simply chapters but rather themes that run throughout.

DR. SCOTT-JONES: Okay.

DR. CHILDRESS: But we have not talked about that. Any comment --

DR. SCOTT-JONES: Then I can hold off on it.

DR. CHILDRESS: No, I think this -- before we get into this, why don't we go ahead and make any comment about the -- the question has to do with the placement of the historical chapter, chapter two. Did you want to make a comment about it?

DR. SCOTT-JONES: I am not sure. I guess it is okay to hold it until we finish our discussion but I think we should consider where it belongs because I think it fits great as it is. I am just not sure about the

transition from one part of the report to another.

DR. CHILDRESS: Yes. We will certainly need to work on transitions but any quick thought about the placement of historical discussion? We had some discussion of that last time and thus it became the second chapter.

MS. CHARO: Jim?

DR. CHILDRESS: Yes, Alta.

MS. CHARO: I think it may be difficult to make comments about it now because in light of the last round of discussion it may turn out that the historical chapter will wind up being folded into that because of the need to provide explanation for the assertions that underline this vision of a kind of synergy of factors so maybe it makes sense to just leave that until Jonathan has had a chance to struggle with the writing problem.

DR. CHILDRESS: Okay. All right. Arturo?

DR. BRITO: We are up to chapter three now.

DR. CHILDRESS: And again it is not simply chapter three but rather the way in which these issues about decisional impairment, incapacity and informed consent are dealt with in the document, but especially in chapters marked three and four.

DR. BRITO: Well, I am trying to process a lot of what I heard this morning and relate it to this

subtopic, I guess. The difficulty I am still having is the section titled "Impairment Versus Incapacity." In the context of what we heard this morning about distinguishing between those that are temporarily incapacitated and those that have impairment, and maybe Laurie can help us with this and enlightening us a little bit on this because my previous readings on people that have cognitive or mental illness have been found not to be -- not to be able to consent for their own research.

Is that not right, Laurie? You mentioned something this morning about that you do not believe that to be true. You believe that people that would have mental illness can consent to their own research most of the time. Is that -- did I interpret that correctly?

MS. FLYNN: Yes, that is correct. The people who have psychiatric illnesses can give informed consent most of the time. In other words, they are not floridly symptomatic or incapacitated most of the time, most of the people. There are, of course, some few very unfortunate individuals who are incapacitated a great deal of the time. That population, as Alta indicated earlier, is perhaps worthy of special focus because they are very frequently in institutional care. But most people participating in most research today are not those individuals and they are mostly capable of participating

in consent procedures.

MS. BACKLAR: And there is data to uphold this.

MS. FLYNN: Yes.

MS. BACKLAR: And the McCarthy studies.

MS. FLYNN: Yes, there is a recent rigorous look at this issue that provides support for that premise.

DR. BRITO: So along those lines maybe there should be emphasis on that somewhere in here and I am not sure quite where --

MS. FLYNN: Well, that was, I think, the point of the comment I was making earlier this morning about tone.

DR. MORENO: This is incapacity in particular, right, Laurie?

MR. CAPRON: On page 41 you have impairment versus incapacity but you are saying --

DR. BRITO: Maybe emphasize that point within that --

MR. CAPRON: -- the gradation and the temporal nature.

DR. CHILDRESS: So the end of the first paragraph on 41 -- I think that sentence captures much of what you are getting at but I take it you are calling for a fuller elaboration.

DR. BRITO: A little more elaboration than that general topic.

DR. CHILDRESS: Okay.

MR. CAPRON: I understand the comment differently. It is not --

DR. MORENO: It is decision specific capacity.

MR. CAPRON: It is decision specific and it is time specific.

DR. MORENO: Right. Time in the course of the illness.

MR. CAPRON: In the course of the illness.

DR. MORENO: Yes. Got that. Thank you.

DR. BRITO: Other than that when I initially read it I thought it was -- the organization was pretty good and as a tone I did not find it difficult. Now after I am reprocessing the information and from what I heard this morning of the overall tone so it was taken out of context so right now I do not have any other comments.

DR. SHAPIRO: Could I just ask a question, Laurie? I just want to make sure I can understand the comment. You say most of the people who participate in these as human subjects in these areas are for most of the time they are perfectly capable of making decisions.

MS. FLYNN: Yes.

DR. SHAPIRO: Now, I am just trying to think

of what image that is and it is easy or difficult to know when they are able and when they are unable.

MS. FLYNN: That is right.

DR. SHAPIRO: Is it easy or is it difficult? I am asking a question. I did not mean to --

MS. FLYNN: I am not a clinician but as a layperson it is pretty easy to tell.

DR. SHAPIRO: Pretty easy to tell.

MS. FLYNN: It is pretty easy to tell when someone who has a psychiatric -- long-term psychiatric illness is in good shape and is capable functional and able to understand a process and repeat information and it is pretty easy to tell when they are not organized and able to make those kinds of decisions. Now as a layperson I could tell and I am quite sure that there is a finer way for clinicians to test the limits of that incapacity.

MS. BACKLAR: But there are two things. One is as Paul Appelbaum told us when he was here that understanding works better if the information is given by element rather than all at one time and that is not necessarily different from the general population.

MS. FLYNN: That is right.

MS. BACKLAR: But the other issue is that Appelbaum and Griso (?) have put together what they call a clinical tool to assess patient's capacities to make

treatment decisions and I had hoped that this paper could have been given around today and I think it would be very useful if somebody would xerox it and you all look at it. And within 15 minutes a clinician can assess a person's capacity to make treatment decisions according to this particular tool and the research that has gone on. So that is more data in terms of that.

DR. CHILDRESS: And I think we could build more on the Griso-Appelbaum discussion than we do in this report.

MS. BACKLAR: That is what I had -- one of my remarks.

DR. CHILDRESS: Yes.

MS. FLYNN: The concern just is that there is -- there is a widespread perception that by virtue of the diagnosis of a serious mental illness you are incapable and incompetent all or much of the time, and that is not correct and I want to see greater emphasis over time on engaging and appropriately educating and informing and creating active partnership with subjects in research rather than the emphasis that they are all incapacitated, they are all vulnerable. It is a stigmatizing and it is an inaccurate portrayal of what really exists and it tends to lead us in directions different than the ones I think we want to go, which is to much more effectively inform,

engage and create partnerships with these subjects.

DR. BRITO: And by --

DR. CHILDRESS: I am sorry, Arturo.

DR. BRITO: I was just saying by elaborating on this point we can get back to Laurie's earlier comment, too, about emphasizing that most research and most researchers are not doing unethical research and we do not want to persuade people not to do research and I think by doing this there is more of a positive outlook on it and it is also I think putting a little more burden on -- or the onus of the proof of the informed choice on the researcher would help in that manner also. But I am not really sure where to address this in this or how to address it right now.

DR. CHILDRESS: But certainly the comments that have been made, including the last one about the relational aspects, those can be developed at greater length with appropriate kind of support in this section and with attention to the tone issues that have been raised.

Alex?

MR. CAPRON: Well, I just wanted to note that it may be that Alta's early comment about the need for some differentiation will arise more here because if we are talking about Alzheimer's patients or others with

progressive forms of dementia the rosier picture that Laurie has painted is different. But we are also talking about research that proceeds on the presumption that subjects are free to withdraw at the point where research becomes problematic for them, which is our general presumption research, we have to recognize that that may not coincide either because of the nature of the illness or because of the challenges, and I do not mean by challenge studies alone, but the effects of the research process itself may render the subject during the research less able to exercise that degree of self-protection.

MS. FLYNN: And that is important.

MR. CAPRON: And that is an important point to keep in mind as we talk about procedural protections.

DR. CHILDRESS: Okay. Arturo, anything else?

DR. BRITO: Not right now.

DR. CHILDRESS: Diane?

DR. SCOTT-JONES: I will just make a few comments. I must say that I have trouble getting the sense of this chapter because I had to flip back and forth from pages because my pages were xeroxed in a very odd way so I do not probably have the sense of reading it from beginning to end of this chapter but the main things here are the informed aspect of this and then the voluntary aspect of this. And this is related to a point I was

trying to make earlier, we need to think about consenting to what, not just the person's own internal capacity or lack of capacity. And there is some discussion here, and I think it is very important and might need to be detailed more about how the information is actually presented to the person who needs to give consent. This is true generally not just of persons who have some mental disorder or some demonstrated impairment.

Sometimes consent letters are in very small type but even when I read them myself I miss some of it because it is so difficult just physically to read it so there are all sorts of things like that that can be done to make consent easier. I think the report might highlight that more because remember it is not just a person consenting in the abstract, you are consenting in a specific situation in a specific context so I would probably like to see more on that.

The issue of a consent auditor is discussed in detail here. I am not quite sure how we are going to come down on that in the end or exactly what I think about that but I think that is something that is worth discussion. And then the voluntary nature of this could perhaps use some more attention because we do not think as much about how a research participant may feel a sense of obedience to someone perceived as an authority. They may feel some

emotional dependence on other persons so the notion of whether this is voluntary and you can demonstrate that the person has voluntarily consented is one that we might want to think about more. Again that is mentioned in here in a couple of the paragraphs. But those are my main three concerns about this is consenting in a particular context what type of information is typically given, whether there is actual voluntariness, and the role of the consent auditor if we are to go towards that type of a recommendation.

I believe at the last meeting Harold mentioned something about having a person who represents that population help with the consent process like appear who actually helps with the consent process. I do not know how that would work but I think those are three things that maybe we ought to talk about in terms of our recommendations.

DR. CHILDRESS: Okay. So unless -- at this point unless people want to jump in more -- we could get to recommendations which I have asked people to keep in mind as we went along, but does anyone want to address any aspect of Diane's comments?

MS. FLYNN: If I could just make one comment following up on what I -- her last point. I would believe that it is there -- that there is some utility and if it

is practical exploring the suggestion that I think did come from Harold initially that there may be some ways for IRB's or research groups to involve representatives of the community involved in the research as consultants, as advocates, as providing some input and oversight to the consent forms and the consent process that may or may not be in any way the same as the consent monitoring or auditor that has discussed in other places.

But it is an appropriate kind of an outreach to the community of individuals and their families who are part of this research. There is great willingness, I think, across many of these decisionally incapacitated communities to provide that kind of input and it might help to break down some of the isolation of that research community that Alex has continued to reference his concerns about.

DR. CHILDRESS: Other comments? Harold?

DR. SHAPIRO: I have a comment. It is, in part, taking a step backwards but if this inappropriate now, Jim, I would come back to it later. As I looked at these early chapters there were really some interesting things to me as the history rolls out, as it rolls out through the description -- helpful descriptions that Jonathan has given it.

One is that although for much of the general

public, myself included, Nuremberg stands as a huge kind of event that always colors one's view towards these things but the history -- putting that aside for the moment, but the history is one of extraordinarily well meaning people doing things which in retrospect we do not think really continued to be appropriate. I think that is important to keep in mind here.

It is not that there is a lot of bad -- there are some bad people but it is not like there were a lot of bad people and they are always getting us into trouble. It was that they were very well-meaning people who did things which in retrospect we now think we no longer continue doing and it seemed to me that was a helpful thing that came from reading this all at once.

But the much more important part of this is Jonathan traces from Nuremberg to Helsinki through various other national -- our own national commission, of course, and the other commission which is differing attitudes towards this. I think it would be helpful, Jim, that at whatever the appropriate point is for us to have some discussion of exactly those issues. They have evolved. They have changed. The national commission changed what some previous commissions have changed and so on and now we are going to do something and it may be helpful to see whether we have some agreement or some assessment

ourselves of that evolving history and where we want to focus ourselves on it.

Now that may be something we want to discuss much later. I was not sure whether it should come at this point or not.

DR. CHILDRESS: What do you want to do?

DR. SHAPIRO: I am not eager to discuss it right now.

DR. CHILDRESS: Okay. Let's flag it then and come back to it and let's get -- let's see, Diane, did you finish everything you wanted to get out?

DR. SCOTT-JONES: Yes.

DR. CHILDRESS: So then we will turn to Eric and then we will finish up the discussion of decision impairment, incapacity and informed consent.

DR. CASSELL: Well, my comment is that I am troubled and I am still having Sunday dementia but it really --

(Simultaneous discussion.)

DR. CASSELL: -- it really follows on Harold's point.

Jonathan talks about on page --

DR. CHILDRESS: By the way we are using Jonathan here as a name for --

DR. MORENO: This is the name for the

document.

DR. CHILDRESS: -- for the evolving report.

(Simultaneous discussion.)

DR. CHILDRESS: The evolving report.

DR. CASSELL: The evolving report, not to be ascribed to any individual.

It talks about the standards for the ability -- for decisional incapacity. But there is a historical point that I think is important and that is that in the 1960's when people were talking about decisional incapacity they were talking about something called autonomy in which a person ought to be able to exercise their autonomy. And in those days the idea of autonomy was really a quite naive one that anybody in the same position given that would come up with the same conclusion like a contian way of seeing autonomy. But in subsequent years we are not quite so naive about that and we really know that the environment and the context all have an influence on what somebody is doing at any particular point. I take it that you recognize that in these discussions.

On the other hand what is the consequence of recognizing that? That is our problem. Do we -- and in the 1960's you could give a person a piece of paper and it would not matter if the paper had settled down from the

ceiling, somebody could exercise. But we really know that is not true anymore. So -- and you really point that out. But what is the consequence of that?

So I really think in a way we ought to pick up on the suggestion about the history but also pick up on our concept of what it meant to be -- what it means to understand the nature of the research, to appreciate, to exhibit ability and so forth.

On Friday I saw an 18 year old woman who had been having sex with a previous intravenous drug user, unprotected intercourse -- I mean she used birth control pills but without a condom -- for a year-and-a-half and then she got all upset because she discovered he had another partner and now maybe she could get AIDS.

Well, I am not talking about somebody who is decisionally impaired in any way we might say but most of us would think that is decisional impairment. Her reason, "I loved him."

DR. SCOTT-JONES: That is emotion.

DR. CASSELL: Well, but people who are sick have emotion too and people who want to help have emotion and we have not figured out yet how to deal with that kind of problem and maybe we cannot figure it out. I do not know. Maybe we cannot. But on the other hand I do not think we can entirely duck it and see the historical

difference between the 1960's understanding of autonomy and what might be in 1990.

DR. MORENO: I just want to say I second that emotion.

(Laughter.)

DR. CHILDRESS: Diane has pointed several times now about context, who, what and relationality, and I think put it very well.

DR. CASSELL: Yes.

DR. CHILDRESS: Diane?

DR. SCOTT-JONES: This is what I was trying to say in my earlier comment about whether you can claim that participation is voluntary because there is an emotional relationship that is going on when someone asks you to comply with them. You feel something as well as think. So I think that is really important. We are not just --

DR. CASSELL: Whitehead in the 20's talks about the -- how affect influences sensory input.

DR. CHILDRESS: Now, Eric, let me be clear, would your suggestions then follow the lines that Diane has already proposed?

DR. CASSELL: Yes.

DR. CHILDRESS: Or are you --

DR. CASSELL: No, and also the historical. To pick up and to show that it is not just what Diane said

but to show that it is not --

DR. CHILDRESS: Right.

DR. CASSELL: -- we used to have a different belief because we were just coming to believe about autonomy in this setting and now we are beginning to change. We still believe people ought to make autonomous choices but we have a different meaning by those words than we did numbers of years ago. In part, because a document like this is an educational document. It does not just come up with conclusions or recommendations. It is an attempt to educate a public and to bring them up to the same point that we think we are.

DR. CHILDRESS: I think the distinction in part is whether you are working with an ideal of autonomy that says decisions ought to be made in a certain kind of rational way versus respecting people's autonomous choices which may build in emotion and a whole new --

DR. CASSELL: Yes.

DR. CHILDRESS: -- and the informed consent part of this is really an effort to get at the issue of respecting their autonomous choices.

DR. CASSELL: Well, I --

(Simultaneous discussion.)

MR. CAPRON: Would the gentleman from New York accept the possibility that this is a topic being of

general application that deserves further elaboration and thought by the commission and again that we might in this report signal our recognition that the changed use of the term be equally applicable here but that what we are focusing on here is, as the Chairman has just said, is the question of respect for this group of persons at least at the level that they -- that this respect is accorded to others even if that respect was built on a theory that overemphasize the rational side of "autonomous" choice.

DR. CASSELL: Well, I --

MR. CAPRON: Our educational document that reexplores the other -- and I do not mean to dismiss it, Eric. I just --

DR. CASSELL: Okay. I understand.

MR. CAPRON: I am just worried about trying to do too many things at once.

DR. CASSELL: The gentleman from New York is not an oxymoron.

(Laughter.)

MR. CAPRON: I would stop right there.

DR. CASSELL: I would like to say that you are either in it or you are not in it. You cannot in a way say we are going to address this and later on we will go on without referencing that. If you say in this document this is a larger concern, blah, blah, blah, and we intend

to address it later, fine. But you cannot partly get in it and not --

MR. CAPRON: I would happily see us assign an appropriation of our funds towards that study and commit ourselves to it. I am very serious.

DR. CASSELL: All right.

MR. CAPRON: But without saying that in a topic that is already complex enough that we would take this as the occasion for --

DR. CASSELL: I think we should index it.

MR. CAPRON: Okay.

DR. CHILDRESS: And also suggestions of what --

DR. CASSELL: So we are in agreement.

DR. CHILDRESS: -- suggestions about possible people to write such a paper and we will get it because as we look ahead --

(Simultaneous discussion.)

DR. CHILDRESS: -- and some are already underway, other studies are underway and we are getting the min --

DR. CASSELL: Some more of the discussion.

DR. CHILDRESS: I just got in the one on -- a draft of the one on community for example. So we have others coming in and we have Celia Fisher's paper on

relationality. So we need to -- we are building up now some larger conceptual papers for our work.

Alta gets the final word before the break. Eric is already taking his break.

(Laughter.)

MS. CHARO: Will the gentleman from New York --

(Simultaneous discussion.)

DR. CHILDRESS: All right, Alta.

MS. CHARO: You know in the spirit of always plotting your own course I find myself in this section wondering again why we make the distinction we do between children and those who suffer from a variety of impairments in their decision making ability since most children I know are fundamentally decisionally impaired. It may be species typical normal for their age but they are the nonetheless impaired with respect to competent decision making.

In the struggle to understand that, which I think actually can become useful because it helps to reveal the differences and similarities and the conditions which lead to some reflections in the terms of recommendations, differences and similarities in recommendations, things that you might want to move the attention to also because when you have juvenile research

of people with mental illness you do not want recommendations that will yield regulatory requirements that are in conflict with one another.

I found that actually begins to play back into the idea that in the context of the history and the synergistic effects of the factors that have led to the treatment of people in this area being so inadequate we may need to pay attention to the -- how to put this? I am not doing this very well.

We may need to think about looking at the decision making problem specifically in the context of a person with a particular kind of illness in a particular kind of setting in a particular kind of relationship. Setting being inpatient, outpatient. Relationship being with a stranger PI, with a therapeutic caregiver who is suddenly turning into a PI, with which kinds of family or informal caregivers being second representatives because these are the things that begin to distinguish the situation of those with mental illnesses from the situation of children and may help to understand why it is that certain kinds of protections are triggered in one situation versus another.

So in some ways I think that an effort at page 41 to better spell out why we do not treat children as a subcategory for decisionally impaired, which would make

sense if you were focusing solely on cognitive function, might lead naturally into a discussion about the interaction of these factors as well as the historical treatment of children versus people with mental illness, neither one of which has been very good but it has been very bad for different reasons.

It might lead to some recommendations that will have different triggers for different protections than the ones we are now contemplating.

Am I making any sense or am I desperately in need of more coffee?

DR. MORENO: I am not sure how it would fall out. In other words, all of the factors you mentioned, institutionalization, dependence and so forth are true with children also.

MS. CHARO: Not --

DR. MORENO: But there are other factors I can think of that would not be --

MS. CHARO: But what I am --

DR. MORENO: -- a history of having no decisions for example.

MS. CHARO: When I first wrote the comment on the page I have got to tell you that it was a challenge. Like why struggle to make the distinction? Why not just treat children as a subcategory because almost every

problem that you have identified is present with children as well and yet I know that we make -- I mean, I understand that there are some situational differences that are relevant.

For example, the caregivers in the case of children, being the parental figures almost exclusively, right. I think stands in a different relationship than many family members, particularly peer family members, siblings or parents of older mentally ill patients in terms of the kind of emotional dynamic or protectiveness. It is just a different thing. It is kind of an age dependent phenomenon.

Second, you are frequently -- children have not historically been viewed the same way. They have been viewed as unimportant from a decision point of view but they are not viewed as alien and in some ways distasteful, right, which I think is critical of the distinction of how they are guarded by the caregivers as well as by the PI's.

But an attempt to try and distinguish children from other people with difficulty making decisions I think we may be revealing some of the key -- like combinatorial factors that lead to the recommendations and it may, as I was saying, also lead to some thinking about triggers for particular protections like consent monitors or double consent and things like that. It may not but I just

thought it might be worth struggling harder on page 41 on the notion of impairment.

DR. CHILDRESS: And you will be glad to work with Jonathan along those lines?

MS. CHARO: More effectively than I did last month.

DR. CHILDRESS: We will take the last comment from Diane and then we will go take our break.

DR. SCOTT-JONES: I would just like to say I like what I envision from what Alta is saying about laying everything out but in the case of children I think it is different, Alta, because parents are legally responsible for the children. They have a responsibility and they have legal rights over their children. So they are different immediately.

MS. CHARO: Yes, I agree. But with many people who are mentally ill there is a legal guardian present who has all the same requisites of a parent over a child.

MS. FLYNN: Sometimes it is a parent.

MS. CHARO: And sometimes it is. In fact, probably not infrequently it is the parent. But it might be the parent of a now adult person who has a mental illness and I think that actually changes things. Indeed, it just changes the parent-child relationship.

DR. CHILDRESS: All right. Let's take an eight minute break.

(A brief break was taken.)

DR. CHILDRESS: Okay. Let's go ahead and resume. Is there anything else we need to discuss? I think several good suggestions came out regarding decisional impairment, incapacity and informed consent for putting that discussion in a larger context but also focusing fairly specifically on the relational issues as well. So I think that we have gained some clarity on the directions there. But is there anything else anyone wants to add before we turn to risk and benefits?

Okay. I have Alta, Rhetaugh and Eric. Rhetaugh, since you are the only one here you get to --

DR. DUMAS: I am the only one here. I get my point with my time.

DR. CHILDRESS: You get your's in first.

DR. DUMAS: I think that the -- this chapter reflects the lack of clarity and the contradictory nature of work so far on these issues. As I understand it what we are attempting to deal with are conditions that will justify and those that would probably prohibit research on subjects who have decisional impairment.

I think that what is needed, and this certainly is borne out in the text of the chapter, are

clear definitions of these conditions. So far there are two concepts to reflect the conditions and they are risks and benefits. And in talking about risks it seems to me that the definition is limited to risk of harm or discomfort and it is further qualified, you know, minimal risk and greater than minimal risk.

But if I had to use this as any type of guidance I would still be left to my own devices for determining what is it -- you know, how to detect discomfort, how to measure discomfort or harm, and then I think the benefits are defined similarly. That is if it is something that will -- has a probability of benefiting the subject directly or if it is something that benefits the subject indirectly or not at all.

And I think that there are recommendations that tailor these definitions. Although as I say the definitions are vague. So we might have ways to -- we might have guidelines or even regulations related to these but until we gain some clarity about what it is we mean by the risks and the benefits we will still have considerable problems.

So I think that there is some necessity to be a little bit more specific about the measurement. Not that I expect this document would instruct people how to measure risks and benefits as much as to determine that

they need to be better defined. I am not sure whether this committee ought to get into those definitions but rather say what should be considered in defining them. Some broader guidelines.

I think that relates to my continuing concern about questions like how do we determine risk and benefits. Who determines them? On what basis? And what measures do we have to avoid conflicts of interest and other possibilities of bias?

DR. CHILDRESS: I think you are right to suggest that part of the difficulty here is the way in which much of the rest of the discussion and applicable issues surrounding research involving human subjects, much of the rest of that discussion has failed on this point also and has left things relatively unclear and we are in the position of having to relate this to the way in which minimal risk is understood in relation to children, for example. And the question is how much progress we can make in this particular document.

DR. DUMAS: I tend to vascilate on this. I would like to give people -- I would like to make this document a very clear overview of the numbers and the problems inherent in making decisions about the involvement of human subjects and research in general and the involvement of this subgroup in research more

specifically. And what kinds of conditions pertain in general and furthermore specifically. And then how do we decide -- who should make the determination about the conditions, at what point or points, and then what kind of guidance can be provided for making those determinations.

DR. CHILDRESS: Okay. Before opening it for discussion let me go ahead and get Alta and Eric in on the risk and benefits and we will get all the points out and then see what in general or specific things we need to do for this subject.

MS. CHARO: First, building on what Rhetaugh was suggesting I do not think that in this report we can define minimal risk with regulatory language that is going to be superior to what exists because that is bigger than this report. However, what we could choose to do in this report is to say given the acknowledged problems with the language and the variable interpretations, all of which are referenced in here.

Is it acceptable for this population to continue using those categories at all or should we be searching for a different way to structure the rules governing when you can enroll and under what conditions? And that is a legitimate inquiry. Are the problems with these definitions so overwhelming that we need to simply abandon them versus these are problems, we acknowledge

them, they are generic, they go to deeper issues, not only regulatory language, but in -- as we will talk about this afternoon -- the role of the federal government in helping IRB's and the placement of the organs of government that are going to be doing that in helping to provide definitive interpretations or super adjudicatory powers, et cetera.

DR. MORENO: Alta, I am sorry, I am just unclear. You mean -- by the language you mean minimal or greater -- or nonminimal as the --

MS. CHARO: That is correct.

DR. MORENO: -- trigger for all the other protections?

MS. CHARO: That is right.

DR. MORENO: Okay.

MS. CHARO: So that might be a discussion you would want to engage through here, right. Are the problems big enough that we want to abandon it and go to something that is a straight risk benefit comparison and abandon staging of protections based on definitions of minimal and nonminimal.

Another thing that might be worth doing to help deepen that discussion would be to acknowledge the interaction between minimal risk and things like expedited review so that we begin to see at a regulatory level, at

the local IRB level, the implications of this kind of language for review of human subjects generally and how that would play out. And that -- the beginning of kind of documenting that might make it easier for us to then discuss it as a policy question in terms of recommendations.

The second independent comment, and it will be the last one I make, is on the way in which we think about financial incentives in the context of benefits. We are -- in the discussions beginning on page 83 and going on to 84 -- assuming that monetary benefits are indirect. Monetary benefits are actually so distinct that it may be worth just listing them separately because in this context where frequently there is going to be a second person involved in the consent process, a second person who may be, in fact, exercising some kind of legal authority over the life circumstances and finances of the human subject.

The financial incentive question gets more interesting because however you define direct or indirect the benefit the question becomes who is going to be actually receiving that benefit. This is an issue for children as well. Is it going to be the caregiver who actually receives the benefit or is it going to be the subject?

Now for kids this is a very under examined

issue and yet you can imagine ways around it like the financial benefits would be in the form of bonds that are going to be accruing for the child's benefit at some time in the future and you can isolate the benefit to guarantee the kid gets it. In these cases that is going to be an even more intriguing problem. How do you ensure that what benefit exists goes to the subject? This is not to cast dispersions on the motivations of the family members but especially as you see on page 85 when you pick up towards the end there is some ambiguity about the basis on which a surrogate decision maker when that is the situation we are in -- some ambiguity about the standard by which the surrogate decision maker makes the decision. Is it based on what they think the subject would have wanted if competent in all senses? Or is it based on the surrogate's own independent decision making?

Financial inducements then begin to get particularly problematic. So I was suggesting perhaps we hold that separately from other benefits to allow that discussion to take place.

DR. DUMAS: Maybe there might be an argument for defining financial rewards as putting the person at higher risk.

MS. CHARO: Because of the inducement to --

DR. DUMAS: Because of the inducement.

DR. CASSELL: We do that about papers which --

MS. CHARO: It is possible. I mean, that is exactly what I am saying. Pull it out so that we can think about it slowly.

DR. CHILDRESS: Because direct and indirect does not work well.

DR. DUMAS: Right. No, it does not.

DR. SCOTT-JONES: But it does need more discussion.

MS. CHARO: Yes. The hints are already there and I am just suggesting we go ahead and expand on them.

DR. CHILDRESS: Eric? Risk and benefits, anything you want to add?

DR. CASSELL: I have very little except I want to pick up on, on something Alta said. Ultimately all of these categories get bureaucratized.

MS. CHARO: Yes.

DR. CASSELL: So that, for example, the category of minimal risk got bureaucratized, then blood drawing became a minimal, and it obscures what it was meant to do, what the whole thing was meant to do, which I think is one of the points you were really highlighting. Nobody should participate in something that puts them at a risk greater than any benefit they could get. When you start talking about minimal risks you obscure that and you

obscure it because you give a bureaucratic way out of somebody really specifying am I going to do harm to this patient.

MS. CHARO: Well, see, but you actually do not even mean -- I do not think you really mean what you just said because you would have now just eliminated all nontherapeutic research.

DR. SCOTT-JONES: Yes.

MS. CHARO: You know, research that is purely exploratory that involved a blood draw. Right? Because the risk would necessarily outweigh the benefit.

DR. CASSELL: No, no, no. That is not risk. It is not risk. It is not risk in the sense that the risk with which -- when Alex sends us a research proposal I would say it is not a proposal, it is a piece of research in which people are allowed to be psychotic for a short time. Alex, I do not know why you think that is -- just a few hours of psychosis.

(Laughter.)

DR. CASSELL: And somebody when they reviewed that must have thought that that was low risk. So my point is not going to excuse that, it is to get rid of that so that people focus on risk. Risk is what risk is. These people were put at risk. Not -- it is not equivalent of drawing blood or they were inconvenienced.

It is not inconvenienced. It is risk.

DR. CHILDRESS: But there are different kinds of risk. Risk refers only to the probability of some --

DR. CASSELL: Something --

DR. CHILDRESS: -- adverse outcome they did not know.

DR. CASSELL: That is right.

DR. CHILDRESS: And you can talk about the probability of something negative happening to a number of these. But what we say about the risk has to do with both how probable it is that a negative outcome will occur and what is the magnitude of that outcome.

DR. CASSELL: But then that is what we ought to focus on. If it is magnitude of probability, which of course is what we do in clinical things when you are trying to figure out if something bad is going to happen, it is not just the magnitude, it is the probability.

MS. CHARO: Right. But, Eric, does that mean that a blood draw has no risk. As somebody who has had hematomas that go from my wrist to my shoulder from having a blood draw there is a risk. It may be small but if I were incapable of understanding what had happened and if I suffered without understanding, which might be true for people with severe forms of dementia, that is real. Right?

Or some of the things we review in our IRB. There is a remote problem -- the remote risk that you are going to yield incontinence.

DR. CASSELL: But then you are --

MS. CHARO: You know, to some populations incontinence is a huge issue.

DR. CASSELL: -- you are making the point. You are making the point that if you get it as a bureaucratic thing and you say there may be a hematoma (black and blue mark) and go on. You have not specified what you just talked about. The magnitude of the meaning of that risk to that person is not there at all.

DR. CHILDRESS: Except --

DR. CASSELL: Even though you have specified it in the form.

DR. CHILDRESS: Okay. Arturo and Diane, remember the question is given the material we have and we have had some discussions from Rhetaugh and some suggestions from Alta about ways to deal with this body of material, and I am not sure where Eric's suggestions have gone here, but two quick comments and then let's open it up.

DR. BRITO: Okay. I am not sure where they are going either. The comment I wanted to make was I think the difficulty is in defining -- physical risk is

much easier to define than psychological risk. Like, for instance, I was just briefly looking over one of the articles that Alex gave us on amphetamine induced exacerbated psychotic symptoms.

If you look at the subjects -- the methods section, the second paragraph, gives a statement "All subjects were in good physical health as determined by physical exam, EKG, laboratory tests, et cetera." To me that implies that the physicians doing this study actually thought that by making sure they were in good physical condition that there is no risk. So the problem becomes defining minimal or above minimal risk, et cetera, and that is the problem, is defining what truly is a psychological risk.

There have been studies on blood draws in children looking at the long-term psychological risk, et cetera, and that is in essence what we are talking about, and a lot of -- and what we are really talking about doing is research on mentally incapacitated individuals which we know very little about. That is why --

DR. CASSELL: Well, I am trying --

DR. BRITO: -- I think I saw -- are we going to get into -- are we going not get into actually defining what risk is? I misunderstood what you were saying there, Eric.

DR. CASSELL: I am trying to go back -- well, let me try and make it simply -- I mean, simplify it for myself. What has happened as a result of previous categorization of levels of risk is a bureaucratization of it that obscures the basic concept of risk so that ultimately the researcher is not focusing on what is my responsibility but towards this person -- that is what risk -- you know, when somebody is at risk --

DR. BRITO: Okay.

DR. CASSELL: -- somebody else is responsible.

DR. BRITO: Right.

DR. CASSELL: If there is no risk the responsibility is diminished in that sense. So that it has gotten people away from focusing on their responsibility to avoid harm to a research subject or at least make a research subject know the extent of harm possible so that they can make an informed decision about participation in this research.

MS. CHARO: Eric, actually I think I misunderstood you before and let me try out again what I think I -- let me use an example. We were reviewing a protocol that had to do with interviewing people and at one point you asked them about suicidal ideation. It struck us that although that question might be benign in most of the population, but for somebody who actually has

been on the edge, that simply asking the question might, in fact, begin to trigger thinking about it in a way that was dangerous. And we asked the PI to help us come up with some literature discussing the phenomenon of suicidal ideation following a discussion about suicidal ideations so we could understand what risk this survey actually posed to this population.

So maybe in some ways what you are talking about imbedding the discussions about minimal risk versus nonminimal risk perhaps more closely in the discussion about the need to individualized the discussion of risk first to this particular population being studied and then potentially to the particular subject being recruited and in that way begin to go away from the suggestion that people have made of having classic examples of things that will always be reviewed as minimal risk and instead return again in each case a context specific examination of whether there is minimal risk here for these people.

Am I now capturing --

DR. CASSELL: Yes, much more so.

MS. CHARO: But not quite then.

DR. CASSELL: Well, I think you are and I think its meaning is being obscured. The word "risk" is -- risk is a probability of harm. And it is that that has gotten obscure. The word "risk" has moved away from the

probability of harm. Now there are harms I am willing to endure for good, right, and --

MR. CAPRON: But the word "risk" usually also encompasses the negative --

DR. CASSELL: Yes, that is right.

MR. CAPRON: Harm over two dimensions.

DR. CASSELL: And has a magnitude of a probability.

MR. CAPRON: Yes.

DR. CASSELL: And that has gotten obscured in what followed and I think might not have been possible otherwise. It may be we will not solve it either. But the researchers should be knowing that that is the researchers' responsibility to make sure that they have assessed what harms are coming to this subject because of what you are doing and then your question there in a population of people who might commit suicide that question is not benign. That is not a benign question.

DR. CHILDRESS: Before I get to Diane, let me just note that it seems to me that several of these suggestions have focused on the way in which we can emphasize the context of informed consent and the context of risk analysis. So that, I think, is an important way for us to think about the evolving draft and I think all those suggestions should be taken very seriously.

Remember we are focused on this particular chapter and seeing what changes we want to recommend and we want to spend -- our two speakers for the discussion of imaging research and other issues and research involving human subjects with decisional impairments are already here. We are running -- going to run probably about 15 minutes behind. If you folks can bear with us we appreciate your coming. We will try to get some of these other issues out for purposes of revising the draft.

Diane?

DR. SCOTT-JONES: I have a few comments about this chapter. One of them has to do with what Eric was just saying earlier about risk being the probability of harm and I think there is a problem in the language that is used when we use "risk/benefit" instead of "harm/benefit" because the risk/benefit does not in and of itself convey a probability so you have to use the term "expected benefit" or "anticipated benefit" the way Jonathan does in most of the chapters. I think that is really an important distinction because when we use risk/benefit it sort of implies that somehow the benefit is somehow guaranteed instead of a probability, the same way risk is, indeed, a probability of harm occurring. So it would be better if we said harm/benefit to use terms that are more parallel to one another.

And then also Jonathan has done a great deal to talk about how one might well define what risk is in specific cases or what minimal risk is and I think that is consistent with what some people in the research world on children are doing. We are talking about a standard of decent treatment to replace the notion of minimal risk tied to the circumstances of an individual's life. So you have a standard of decent treatment in research instead of this shifting notion of minimal risk tied to individuals' own lives.

I think also when we talk about the benefit of research we have to remember that research is research. If we knew the answers for sure we would not need to do the research. So the notion of benefit is already qualified when you put it in the context of research because research always has uncertainty in it or it would not by definition be research. So we have to be careful not to overplay the notion of benefit, direct benefit from research. And if we are in our society creating some new entity that is not research and not treatment but some entity in between those then maybe we ought to be clearer about that because research does not have known outcomes or it would not be research.

DR. CASSELL: Just put the word "probability" in. Once you do that you put the word "probability" in

just as we have in risk which is an abstraction for probability of harm. Benefit is an abstraction for the probability that good will come.

DR. SCOTT-JONES: No. Benefit in and of itself is not. You have to say expected or anticipated benefit.

DR. CASSELL: Yes, but I mean in research --

DR. CHILDRESS: I am not sure that is done.

DR. SCOTT-JONES: Yes.

MS. CHARO: But, Diane, you do need to clarify this. There are subcategories of research where benefit is known to be probable, not just possible. You can have comparisons between two standard known to be effective treatments --

DR. SCOTT-JONES: Exactly.

MS. CHARO: -- in which you are looking just to find the relative degrees of efficacy. So there are going to be subcategories where this is not true and where you really have genuinely therapeutic interventions that are simply being compared.

DR. CHILDRESS: Any last comments on risk and benefits, this revision? Trish?

MS. BACKLAR: That old problem with children and that is when we talk about minimal risk are we talking about people who are healthy, are we talking about people

with minimal risk for people who are ill, and we need to make sure we make a decision about this, and I am concerned that we keep that risk is -- minimal risk means that kind of everyday risk for a healthy person.

DR. CHILDRESS: Any response? Jonathan?

DR. MORENO: I would welcome the opportunity for the advisory committee to get on record -- advisory commission, excuse me -- to get on record on this issue because this is something that really is a problem. The shifting standard or shifting interpretation of what counts as minimal risk. I really think just speaking in my professorial role and as a staff consultant I think this is an important issue NBAC really needs to get into, whether here or on some other report.

DR. CHILDRESS: Well, and it is something that is general topics that cut across several areas for the purposes of contract papers. It seems to me this is one that cries out for it as well. So we would welcome suggestions from people.

DR. MORENO: And it relates to Alta's first comment a few minutes ago with respect to risk categories. My concern is that if you really want to raise the deep question of whether these risk categories, this nomenclature ought to apply to these populations of specific concern in this report, that is a much -- there

is no reason to isolate that only to these populations and that is a big discussion which --

MS. CHARO: But the point simply was if you think the categories are so broad and so subject to manipulation, that for this population for which we have already identified lots of other reasons why they tend to get over enrolled or inappropriately enrolled or whatever, you may say to this population in particular we are going to say you cannot even use the categories. That is an option. I am not suggesting it necessarily but it is an option.

DR. MORENO: You can strongly suggest though that this subcommittee is going to follow up that problem with respect more generally to the regulatory scheme.

DR. CHILDRESS: Let me call this one to a close and let's turn to procedures and let me start -- sorry to have to cut it off but I am conscious -- first of all, let me say I have two people on the list to testify during the public testimony period. If you have not put your name on the list and are hoping to testify do let me know because we are going to have to structure the remaining time this morning to be able to accommodate people. If there are only two we will not get to until probably 11:20.

DR. MORENO: The subcommittee members should

be clear that they are not going to see another draft of this December 3rd unless you want to pay for my child support.

(Laughter.)

DR. CHILDRESS: No. Our understanding would be that on December 3rd when several of us from the subcommittee will be gathered to try to reflect on what has been gained from the second and third discussions at the National Institute of Mental Health we will be working from this draft and trying to incorporate things here. Then the next draft after that, which by the way we want to put changes from this point on -- given the way that we have now read this -- let's put the new material in bold or something so that people can really concentrate on what is new and not have to reread. I think we will be at that point. Because there will be a fair amount of new material with the discussion on the 3rd and what Jonathan incorporates given our discussion today as well as subsequent suggestions.

Okay. Henrietta reminded me that the meeting of the National Institute of Mental Health, that session is a work group and not a public meeting. This also reminds me to ask since several committee members have raised it, are those of us who are planning to attend fully registered and duly accounted for, and all that.

Could you check on that and let us know? We have not done anything other than reserve the hotel room but we need to just make sure that all of us are properly included.

DR. HYATT-KNORR: You mean at the NIMH?

DR. CHILDRESS: Right. Right. So if they have limited space they are aware that we will be present.

Okay. We have been looking at procedures and we will just be able to hit the key points for purposes of working on another draft. Alex and then Alta, and then Trish.

MR. CAPRON: I think that the advanced directive discussion is very helpful and I guess I would like to see us there tease out a little bit more the range of categories that we think are going to -- Trish is signalling to me from her paper we have a basis for this discussion of research advanced directives.

There were a couple of small points -- I might as well just put them on the record -- where I thought there were some problems. It seemed to me that the consent auditor discussion or the reconsent procedures needed further support and a little bit further exploration of the role of the family in this process. I think we also have to begin being a little more specific whether we see these kinds of added burdens or expenses as something that is part of the research process and this

goes to -- this is connected with our broader examination of research.

But it is clear and I think we need to make sure that it is clear in something like our federal report just what a huge enterprise even from the federal side without even counting the drug companies research with human subjects is in terms of hundreds of millions, millions of dollars that are involved. And the notion that part of that should be adequate support so that we do not put on to research institutions and on to individual research subjects the need out of their own pocket to somehow figure out how to protect themselves.

The discussion of wraparound studies has a paragraph that I agree with about the notion that sometimes a wraparound study may be a useful protection but there are a couple of points made there that I think I actually disagree with Jonathan and I want to get it out on the table. I do not think that the coexistence of a wraparound study along with the research intervention is an example of the therapeutic misconception. I think we are in a danger of misconceiving what the therapeutic misconception is if we do that.

The therapeutic misconception arises from a misunderstanding about the purpose of the research part itself. The idea of offering a wraparound study could be

seen as a reasonable or, in light of what Alta was saying about payment before, an unreasonable or undue inducement if the only way you can get real treatment is to go into the research.

I mean that is the Willowbrook issue again in a way. And that is a separate thing. It is not the therapeutic misconception. I mean in some ways it would be quite clear. Here I am asking to be in research. Here I am offering you some treatment. The research is obviously research because I am describing the treatment separately. It ought to diminish the therapeutic misconception. It has a different problem that it raises. I think it is a mistake to mix those.

You also --

DR. CHILDRESS: Jonathan agrees.

MR. CAPRON: Yes, Jonathan agrees.

MR. CAPRON: I do not think this is a matter of arguing. It is just a matter of making -- suggesting that you need to change that.

DR. MORENO: Right.

MR. CAPRON: The other thing is you say wraparound could be suitable follow-ups to certain kinds of -- I am sorry. Reading page 132 at the bottom. Page 132. Wraparounds could be suitable follow-ups to certain kinds of research that involve the provocation of

symptoms. Again that seems to me to be a dangerous statement. If you provoke symptoms it is not that a wraparound could be. You have an absolute obligation to return that subject as nearly as possible if you have not made that impossible by your research to the condition in which the subject was before. That does not seem to me as an example of a wraparound study.

The wraparound I take to be offering some other benefit. I mean, that is not a could be. That is a must. And it is not a wraparound. It is part of the research design.

DR. CHILDRESS: Would you work with Jonathan on redoing this paragraph?

MR. CAPRON: I think -- well, Jonathan, he got that.

DR. MORENO: I got it.

MR. CAPRON: Finally, on the placebo discussion -- this is particularly a difficult question because of the suggestion that we do not really explore fully here about accommodating other federal requirements for drug approval. And I understood, maybe I misunderstood, the fellow who was here from the FDA talking to us about this.

DR. CHILDRESS: Dr. Temple.

MR. CAPRON: Dr. Temple. Thank you for the

name. A cognitive impairment as to names.

To suggest to us reasons why a research design was much stronger and, in effect, cheaper. You could get a lot more information out of fewer subjects if you were doing a strong placebo control because then you did not have the question of what the people who were on the active arm really were showing you and whether they were giving you a stable baseline or not, et cetera.

But I did not understand him to say that even the FDA regards that as an absolute requirement. They have a level of expectation of the reliability of the data and reasons why that data is usually much more reliable when it comes out of the placebo study. But it seems to me that we ought to be a little clearer, and I may be wrong in my understanding, but we ought to be a little clearer about the difference between a predilection towards a particular kind of design and something which requires an explicit exception or is just beyond exception because it goes against the regulation.

And again it becomes a particular issue where people have chronic conditions which can be exacerbated by being forced to be on a placebo arm and so forth. Where we ought to clear as an ethics group looking at this that one is always talking about choosing between benefits and harms or among harms or among benefits. It is not as

though it is black or white one way or the other.

Anyway, so I just would like to have that discussion revised in light of those comments. Thank you.

DR. MORENO: That equivocation, Alex, has to do with the perception at least among many investigators that the FDA may say one thing but do another as you know.

MR. CAPRON: Yes, but then --

DR. MORENO: But that is the point that is made.

MR. CAPRON: -- then we need to dig more deeply into it and have a more definitive statement and either say to people you are right and the FDA needs to change or you are wrong, you are over reading what the actual regulations are, you are dealing with a predilection. So this is not --

(Simultaneous discussion.)

MR. CAPRON: It is a question -- yes, it is a real question of what is the factual base. As I say, I may have misunderstood Dr. Temple. I thought it was a very informative presentation he gave us which was actually in the context more than we were looking at the AIDS issue, I guess. But, yes.

DR. CHILDRESS: Thanks. Okay. Very briefly let's hear from Alta and Trish on suggestions for the procedural discussion and I should emphasize that I have

talked to Jonathan already about exploring possible ways to group some of these so we do not have such a laundry list and see whether some of these might be grouped under a heading of consent or reconsent or something. He is going to explore that for the draft.

MR. CAPRON: This includes what follows on page -- does this include chapter 8 or not?

DR. CHILDRESS: If you want to make some reference to that as well because we do talk about procedures there of various kinds, special protections.

MR. CAPRON: No, I am going to hold off.

DR. CHILDRESS: Okay.

MS. FLYNN: May I make a comment about the last point?

DR. CHILDRESS: Okay. Laurie wants to do a tag on, on the last point. All right.

MS. FLYNN: Just quickly. I want to reinforce and agree with Alex that we need much more discussion of the placebo issue and that there is substantial information that I think would help and we can try to get it to you.

The other thing that I did not see here that we may want to consider and that the national organization I represent has adopted as a policy is that where there has been participation in a placebo controlled drug trial

that it is ethically mandated that all individuals who have a need for improved response should have -- somewhere in the study and at the conclusion of the study if they have responded well to the experimental therapeutic that they should be permitted to continue it until such time as the source of funding can be found for it so that you have sort of two points there.

One is that everyone should have a chance on the experimental medication, even those who may be assigned into the placebo arm, so that everyone gets a shot at what may improve their care. And that once the study is over then the drug company has an obligation to continue all those who have responded well on the experimental drug until such point in time as they secure a source of funding, usually when the drug is approved, can be found.

DR. CHILDRESS: Can you give --

MS. FLYNN: I can send you wording on that.

DR. CHILDRESS: All right. And others too because there will be a lot of things we are not going to be able to touch on obviously in our short time today. If you could send stuff to Jonathan and ask for incorporation in the next draft.

So just a couple of minutes, Alta and Trish, for your final comments.

MR. CAPRON: She passed.

MS. CHARO: I guess I will do it now.

DR. CHILDRESS: Oh, you passed. Did you pass?

MS. CHARO: I was hoping to get in a final comment after we do these.

DR. CHILDRESS: Okay. Trish?

MS. BACKLAR: I think that perhaps at this point I do not need to go into this. We are going to talk about the research advanced directive. I do want to say that the way it is right now in the document that suddenly we come across this. There is very little before that has referred to it. There is a little bit about it. And then afterwards we do not use it in any way to --

DR. MORENO: To come back to the recommendations.

MS. BACKLAR: -- the recommendations. And I think that we need to find some way to integrate it and also for people to be very aware of one of the big problems that is there and that is in terms of the after care which one might get into the wraparound studies of who is going to pay for that after care, particularly as we move to managed mental health care. So that is a big issue.

DR. CHILDRESS: Okay.

MR. CAPRON: We do get to it in the

recommendations.

DR. MORENO: I do cite it in the recommendations.

MR. CAPRON: State law, we recommend that state --

DR. MORENO: State's model.

DR. CHILDRESS: That is right, consider the state model. That is a really good point. I have raised with Jonathan the issue of how we get into chapter 7, too, and propose that something -- that he try to work up -- that he try to work up an introduction.

MS. BACKLAR: I am sorry but there is one thing that I think that is important that maybe is not spelled out enough about this particular model and you may have had my original paper which I sent to everybody on it. And that is that I perceive that this is a way to do this that does not burden down the regulations. It can be incorporated but becomes the responsibility of the research community to see that this is done.

DR. CHILDRESS: Well, thanks, everyone. There is a lot more to do. We will try to get some of it in today but we have had two very patient guests and since we had hoped to start with them about 20 minutes ago, and we are very happy to have with us today Dr. Carol Tamminga of the Maryland Psychiatric Research Center and Dr. Trey

Sunderland of the National Institute of Mental Health and also chairs the National Institute of Mental Health IRB if I recall correctly. So we are glad they could join us.

I have asked each to speak no more than ten minutes at the outset so we can then have time for interaction.

Dr. Tamminga, we will start with you. Thank you again for joining us today.

DISCUSSION OF IMAGING RESEARCH

DR. TAMMINGA: I am very pleased to be here and appreciate the work that you as a committee are doing. I am a psychiatrist at the University of Maryland and I do schizophrenia research. I do not do private practice. I am 100 percent university employee.

The nature of my -- and I have been doing schizophrenia research for probably 15 or 18 years. The nature of my research has been highly experimental for the whole time that I have been doing it. I always fall into the maximal risk IRB categories. And the point of much of my research, the goal of much of my research is to actually look for mechanism in schizophrenia.

My research has actually been focused almost exclusively on schizophrenia and on looking for a mechanism. So the research that I do is often times not of any direct benefit for patients.

Imaging research, which Dr. Childress had asked me to address, is often times not a benefit to people. The only -- I was sort of searching while I was listening to you discuss of what benefit imaging could possibly be for the person and an example of a normal control struck me who took the PET Scan, took her own PET Scan, put it on a Christmas card and said, "Thinking of you at Christmas," but that is --

(Laughter.)

-- that is about the only example I can think of.

I think that schizophrenia is one of the -- is one of the only medical diseases that is left whose mechanism and whose etiology are entirely unknown. The treatments that we have for schizophrenia, as all of you I am sure have discussed before, are symptomatic treatments. They are like aspirin treats a headache. They are not curative treatments. They are not treatments like insulin for diabetes. And consequently looking for pathophysiology from my point of view is the only way that we are going to be able to really find out what the mechanism of the illness is and move to specific treatments that treat that mechanism.

In the area of schizophrenia research opportunities might be at their highest point for sure in

the last 20 years. Basic neuroscience has provided us with a lot of information about how the brain actually works. So that there is a lot of opportunity to take very sophisticated knowledge and apply it to a disease.

I asked myself the question what makes schizophrenia research so challenging? So what really makes it -- what makes schizophrenia research really require such contributions from a schizophrenic person? And first of all it is brain research and the brain is of course a buried organ. There have not been many ways that we could tell how the brain works until recently and in my opinion brain imaging, particularly functional brain imaging is one of the ways in which you can actually -- we can actually see how the brain solves a problem and how the schizophrenic brain takes the same problem and solves it or does not solve it.

Another thing that makes schizophrenia research very challenging is that it is a -- as far as we know -- uniquely human disease. I have heard people, basic scientists argue whether or not a mouse could have schizophrenia but since I am a clinician I think it is kind of a useless argument and we have no animal models of schizophrenia and questions of mechanism can really only be answered in the schizophrenic person with their -- in research with a schizophrenic person. So that

schizophrenia research just of necessity requires that we elicit both the informed consent and the cooperation of people with schizophrenia in order to pursue the research.

So that from my point of view schizophrenia research needs both the permission and the cooperativity of people with schizophrenia. And this implies attention to the process of informing the person, to the process of obtaining their assent to do the research, and then of an ongoing -- of assessing their ongoing cooperation or assent with the research.

Now I am sure that you have just spent hours and hours and hours talking about informed consent for the decisionally impaired and the only small piece of that I can talk to is informed consent in schizophrenic people who are decisionally impaired. In my experience and I have had a broad experience only within schizophrenia the decisional impairment in people with schizophrenia of a particular kind. Schizophrenics have some difficulty taking in information. Once they get the picture or have all the information they can characteristically make reasonable judgments or they can characteristically make judgments and work with that information.

In the way that many investigators like me have just not been required to but have over the years learned to gain informed consent it is clear that people

with schizophrenia need information presented to them on multiple occasions slowly, concretely and with examples, and by different people, not only the doctor but also a nurse, a family, multiple people giving them the information. And then they can -- after a period of time they can document that they can take in this information and then make judgments about it.

Although most of us have been sort of working by the seat of our pants for these previous years, now that issues about informed consent have come up people have begun to do research and actually assess when it is that people with schizophrenia actually learn something about a project. We have been doing some research at our institution with informed consent and with documenting that people really actually have information and I have some papers here that I would like to leave with you.

There is one experiment that we have done in treatment resistant schizophrenics and these are people who have schizophrenia who have been chronically hospitalized who probably have the worst of the cognitive deficits of any of the schizophrenics that we elicit in research.

This was a process of informing patients about a rather simple drug-drug study so it did not involve a placebo period. But nonetheless the process of informed

consent is the same for us in that study as in any others and to assess this informed consent we set up kind of an educational process. One of the nurses had designed a sixth session informational process and the patients actually were educated.

At the end of this education period out of 65 patients 95 percent or 62 of the 65 passed a simple test. We have what is called an evaluation to sign consent form with five questions on it talking about the information about a project and patients are required to know these five things about the study.

And 62 of the 65 patients passed of the study. Of those 62 people 80 percent agreed to go on to the study and 20 percent -- excuse me, 81 percent agreed and 19 percent disagreed. So at least it is some evidence that first of all people with -- chronically institutionalized people with schizophrenia can actually listen to information and can learn information if it is presented in the right way. And also that once people learn this information they do not always say yes.

I just want to say a little about what I think the system needs. Clearly as research -- as people start to think about the process of research many problems come up and I will just list out for you what I think is needed to ensure informed consent in schizophrenic people and

ethical research.

I think that the IRB oversight is very important for our research process. The IRB in my institution has become a much more mature institution over the last 20 years of my interacting with it. It has become an institution that -- the IRB has become a committee in the university institution that takes some independence from the individual projects and the persons of the investigators.

It is -- and its oversight is very important and I actually worked interactively with my IRB on several projects that I have had that are quite experimental high risk projects so that the IRB literally looked over my shoulder every -- every three people who were entered into the project and that is actually useful for me as well as an oversight function for them.

I think that if anything might be needed it might not be that all IRB's work at the same level of sophistication and maybe some information, guidelines, some recommendations for IRB's might be appropriate. There is one sort of bothersome thing about IRB's that I -- I am really talking about university IRB's. The question about these private IRB's is I think a big question. There have sprung up private IRB's around the country and I think there is two or three of them that

approved projects that are independent of a university.

What I am saying about IRB's, I do not know that I would extend to private IRB's, and perhaps Trey may have some additional things to say about them, but I think that private IRB's are of more concern because they are not accountable to university systems.

Another thing that I think is really needed is some investigator education. Doctors are really not schooled in ethics. In my day when I was schooled I was not schooled in ethics and I was not schooled in ethical research. Everything I know about ethics I learned from my grandmother and it probably -- probably both at the level of the medical student and the resident, of the research fellow, of the university researcher, and even of the practicing physician some schooling in ethics would be very important. And the reason that I can say that it could be really important is because NIMH has already started strongly suggesting if not requiring that those of us who do research and those students who are trained in research actually are also trained in ethics.

There are courses in ethics that are set up now that I have participated in. You know, being sort of grandiose sometimes I think, "Gee, I cannot learn anything about ethics from a course like this," and lo and behold. The ethics courses -- not only did I learn things from

them but there is -- some of the courses include sort of group discussions around particular case examples and are really very -- I found them very useful and I think myself and a lot of other training programs now utilize them all the time. When NIMH reviews training grants, training grants are almost not approved at all unless they have courses in research ethics.

Then, of course, family involvement in the whole research process is very important and is one thing that I have always used to make sure that family members or that people closely associated with the person know about the research, receive protocols, know the risks and benefits. We are not allowed to solicit family consent for the research because research subjects are competent. The research subjects that I use are competent. But for sure the family can act as an ombudsman for the patient.

That really brings up just the small caveat that we can discuss more later that not every schizophrenic person is probably appropriate for research and that proper research settings need to be set up in which to conduct research and those sort of are assumptions of all the rest of the things that I have said.

Thank you very much.

DR. CHILDRESS: All right. Thank you very

much. Why don't we just take a few comments or questions at this point and then get Dr. Sunderland and then talk with both of you together. But first any quick comments or questions?

Alex?

MR. CAPRON: When you described your work as the high risk research, you do imaging studies?

DR. TAMMINGA: I do imaging studies.

MR. CAPRON: And in the imaging studies the high risk is that you want to observe the brain when the person is off the neuroleptics. Is that what the risk is? Or is it the going into the machine that is risky physically or psychologically? Can you just elaborate because we were having a discussion of what risk was before and I wondered how you use the term?

DR. TAMMINGA: Right. For almost all imaging research -- some of our imaging research is not done in drug-free people but most of it is done in drug-free people. It is really necessary in imaging research if you are looking for what is associated with an illness to take away everything but the illness so you can see what is associated with just the illness. So most of the people -- so being in a medication free state and being in a medication free state for a relatively prolonged period of time since antipsychotic drugs have rather long half-life

so we characteristically do washouts of two or three, sometimes four weeks.

These are hospitalized people in a research study so whereas they do not get antipsychotic treatments they get other treatments but they are drug free. I use some probe medications, some medications that actually increase psychosis. So under a PET scanner you can see what a psychosis increase looks like with a medication like ketamine. Somebody had mentioned that before. And what the brain looks like with an antipsychotic drug that decreases psychosis.

MR. CAPRON: So you are using the word "probe" the way the word "challenge" has been used.

DR. TAMMINGA: Um-hmm.

MR. CAPRON: The other question that I raised before when it was suggested by Laurie that we have -- we ought to recognize that people who are psychotic have periods perhaps on their medication or otherwise when they are quite capable and the process that you described indicates how you would assess that and encourage it and break things down to make it possible for them to consent, quite capable of giving consent. e of giving consent.

And then you describe three or four week washout processes and I was concerned how we deal with a change of mind because if I am in a research study and I

do not like it I can get out of it. But if my change of mind is ascribed by the people around me to the fact that I am now in a florid psychotic state what happens then and how particularly would something that would require cooperation, which is the second thing that you emphasized, not just the permission but also the cooperation, how do you deal with that?

I mean, it must occur that sometimes by the time you get ready to put the person in a PET scanner they are by then delusional or hallucinating or in an angry mode, an aggressive mode, or I mean something. What is your experience with that? How do you deal with that? Do you -- at that point if they say, "I do not want to have anything to do with it," are you bound to listen to them or do you seek consent and continuing permission from someone else? Do you treat them in some way that would sedate them but not obliterate the psychosis so you could still study them? What happens?

DR. TAMMINGA: Well, that question is a little easier to answer from the point of view of imaging because so much cooperativity is required. Schizophrenics have different ways of saying no and one of them is saying, "I do not want to go into the scanner." We actually give schizophrenic people a lot of experience with the scan room and an opportunity to get into the scanner on their

own and some familiarity with the instrument. It is a bit of an intimidating room and stuff like that. That is before we do the project.

If they say, "No, I do not want to do this," or if on the day of the scan they look at the scanner and say, "No," as did one of our people because we were going to take a look at the family shield in her brain, we were going to see a picture of her family shield, I mean that is no for us and so we do not proceed with the research.

And I think that most people do the same thing so that the ongoing assent is really given by cooperativity.

MR. CAPRON: Do you -- have you ever published on that subject giving numbers of recruited subjects? You just gave us, for example, the 81 percent on the 62 who got through the knowledge level and then 19 percent said, "No," and 81 percent said, "Yes." Have you ever looked back and for the information of the field published on your nonassent rate as well or has this ever been a subject? Do you know of others who have addressed that?

DR. TAMMINGA: I do not -- I cannot -- I certainly have never published on it myself. I would guess that somewhere between five and ten percent of the people that we take through this scan process. I work on a research ward so that the people who come to the -- come

into this inpatient setting already know that research happens there so that they are already somewhat in the -- in a research mindset or cooperative with research before they come.

MR. CAPRON: Right.

DR. TAMMINGA: And then we do everything really by process and repeated exposure and if they want to go down to the scan with one of their peers and watch it just so that they can see what happens before they starts. And none of us have really -- I have never really published on it, no.

MR. CAPRON: The only reason I ask is in the other washout studies that we have seen certainly the problems that are described of people who are in the washed out phase of the drug include such manifest psychotic symptoms and particularly senses of persecution and the like that it just is surprising to me that even if someone who is being treated for schizophrenia comes to your unit knowing its research and wanting to participate that you might not see a fairly high percentage of them by the time you have washed them out and three or four weeks have gone by and when they are not getting their medication that they would not have more problems of them saying, "No, you know, this is not -- what are you doing?" And you described the one woman who was -- she thought you

were going to be looking at her family shield or something. I mean, whatever it is.

But I am just surprised that this is not a common phenomenon. That is why I wondered if it has been written --

DR. TAMMINGA: There are people who do not agree to the research from the beginning.

MR. CAPRON: Yes, I understand that.

DR. TAMMINGA: And I was not including those people.

MR. CAPRON: I understand. But it is the ones who agree before you wash them out and then once they are washed out and they are back in -- at least some percentage of them just by the cycling of the illness would be --

DR. TAMMINGA: See, when a schizophrenic becomes psychotic or when they have some return of their symptoms it is not as though their whole mind is consumed by the symptoms. They might have -- they might have the delusion that the food is poison but they do not have the delusion that everybody is trying to kill them all the time. They might have hallucinations and feel that God is speaking to them but they do not -- but there are still many other aspects of their mind and of their judgment that they can bring to bear on other questions. So just

because schizophrenic people have florid symptoms does not mean all -- sometimes it happens but it does not always mean that those symptoms completely take over their minds and their judgments.

MR. CAPRON: That is very helpful. Thank you.

DR. CHILDRESS: We will take three quick questions. Actually four. I have Eric, Diane, Trish and Alta. Okay. We will need to make them quick.

DR. CASSELL: How many times does it happen that a person who gave consent and then told you that they wanted to go back on their treatment? Half way through your project they said they had enough and they wanted to go back on treatment. What percentage of the time does that happen?

DR. TAMMINGA: It is rare that a schizophrenic says they want to go back on treatment. Neuroleptic medications are unpleasant to take and some of the reasons that people actually come to our ward is so they can be drug-free. It is not unusual to have somebody say that they want to stop a research project. They may not like a drug. They do not like the effects of the drug. I would guess maybe ten percent, fifteen percent, twenty percent. They do know that when they stop a research project they will eventually get back on treatment. We work with them around the treatments that they want.

DR. CHILDRESS: Diane?

DR. SCOTT-JONES: When you are reporting your studies do you report the number and percentage of the participants who wish to stop and you allow them to stop once the study has begun? Do you report that rate?

DR. TAMMINGA: I do not. In my grants I report that.

DR. SCOTT-JONES: Right.

DR. TAMMINGA: In order to --

DR. SCOTT-JONES: So one can go back and get that information.

DR. TAMMINGA: Oh, yes. I am sure -- it is important to know for scientific reasons as well as ethical reasons.

DR. SCOTT-JONES: Right.

MS. BACKLAR: That is what I wanted -- two things I wanted to say is that you must have some record.

DR. TAMMINGA: Yes.

MS. BACKLAR: So that would be very interesting for us to know if that is not too terribly difficult.

The other question that I have is how do you go about recruiting subjects for this kind of research?

DR. TAMMINGA: We do keep careful records so it would be easy enough for -- it would be maybe not easy

but it would be straight forward for me to get information if you wanted some additional information.

DR. CHILDRESS: It could. That would helpful to give us kind of a picture.

DR. TAMMINGA: Sure. We recruit people to come to our inpatient research unit usually very slowly and I think this is not uncharacteristic of research projects. People who are looking for an alternative to usual treatment. First of all, they have to need inpatient hospitalization. They have to be looking for an alternative for some of their current treatment. Then we invite them to come and see our place and listen to the kind of research that we usually do. We tell them about the research that happens on the unit. We let them look around and we let them meet the nursing staff. We meet them and their families. We look at their records.

And if they have an interest in participating in research and if they are not put off or whatever by the kind of research they hear about then they come into our research unit. Nobody is really required to sign informed consents before they come but we do want them to listen to what kind of research commonly happens here so they gain some familiarity. And then they come into our inpatient setting and they accommodate to it for a month or two and then we present them with the research protocol that we

think -- or a research protocol that we think would be important for them or would be -- into which they would fit and might be something that they could participate in.

And then a number of different people from the unit present the nature of the research. We talk to their families and caretakers about the research. We encourage the families to get outside information of whatever kind about the protocol or the patient for that matter.

We had an interesting experience. One time earlier in my career I worked part-time at the NIH in the Neurology Institute and still worked at the University of Maryland ward I was talking about so I had encouraged one of my families to call around to find out about this particular medication. They called up NIH and they were referred to me at NIH so that they wound up talking to me at NIH about -- I referred them to somebody else. But we really encourage people to -- families and the schizophrenic person themselves to be thoughtful about it and then they sign off. That is sort of part of the informed consent.

MS. BACKLAR: I forgot to thank you so much, Carol, by the way for coming. We really appreciate that.

Do their physicians sometimes send them to you? Does that occur? Their psychiatrists send them to you? Is that one of the ways?

DR. TAMMINGA: Well, what happens sometimes -- mostly in our dyskinesia clinic, which is a tertiary care clinic, because then the schizophrenics retain a relationship with their primary physician. If any primary physician or psychiatrist refers us a patient we are mighty pleased and would talk to them. We do not usually get people that way. Schizophrenic people who are lucky enough to have invested physicians often times are doing pretty well on the outside.

MS. BACKLAR: That was -- my final question is after care. How do you -- what are your procedures when you are finished using some of these in research?

DR. TAMMINGA: Well, we first take our time. We first get them back to -- we first treat them clinically and we usually take three or four months in doing that. One of the luxuries of the unit that I have is we do not have any length of stay requirements.

MS. BACKLAR: And what are the issues to do when they refuse treatment when they are inpatient? How do you deal with that if they refuse treatment? In other words, refuse to go back on medication how do you deal with that and get a civil commitment?

DR. TAMMINGA: Well, we do not -- on my particular research unit we do not have any people who are not legally competent or people who are involuntary

admissions. Initially we would really try to work with them and we would go through the variety of antipsychotic treatments with them, some of which might include medicine and some of which might not, and we would try to invest them in one kind of treatment strategy or another. We would work with them.

I think it is people -- I have never run into a person who sort of flatly refused to take all medication but really they might try this medicine and if they got a bad side effect we would stop it and they would try another medication. Most generally people can get to their most optimal treatment.

Almost inevitably we -- not always, but in many cases when people leave are much better treated and in a much better clinical state than when they came.

MR. CAPRON: Do they ever check out against your advice without taking the treatment?

DR. TAMMINGA: Oh, sure. But they -- but characteristically we do not allow them to check out of our ward against our advice but we would transfer them to another ward and then they would be on a regular ward where research would not complicate anybody's decision of what to do.

MR. CAPRON: And where if they -- that ward might seek civil commitment?

DR. TAMMINGA: Oh, yes.

DR. CHILDRESS: Okay.

MR. CAPRON: This is just -- your exchange with Trish leads me to understand you do not usually see patients referred by their psychiatrist because such patients are usually -- you said are fortunate enough to have their medical care going well. Did I understand that? So the ones who you do see are typically people who are self-referred out of a sense that their own treatment is not going well and they need --

DR. TAMMINGA: Well, they are not self-referred. They are usually hospitalized in another -- in another hospital and referred by the physician. They are referred by the physician of that hospital but it is not like that is the patient's physician. It is just somebody that --

MR. CAPRON: Oh, well, that is a very big clarification. I am glad I asked. That helped. I had a very different impression.

DR. CHILDRESS: Alta?

MS. CHARO: Well, it is clearly on this because a theme throughout all this area has been the portrait of misconception and certainly in the testimony we have heard the frustration of people who are patients and their families have expressed at the way in which they

have perceive results having been treated has been complicated. Whether they expected they were getting treatment or they expected they were research subjects. So I want to understand even more exactly what is going on as people first encounter your ward.

You said to Trish that people come to your ward because they are looking for an alternative which to me sounds like they are looking for a therapeutic intervention better than the one they are getting.

DR. TAMMINGA: Sure.

MS. CHARO: Right. And that you also attempt to assess their interest in participating in research of various types once they get there. Now, I am trying to understand, the extent to which in a sense what is happening is that there is a quid pro quo. You can get an alternative to treatment that you think are the same therapeutic on the condition that you will be somebody who is predisposed to participate in research although for each individual protocol there is going to be a consenting process that will assess your consent for that particular protocol. Am I understanding correctly what is going on? That this is really a -- this is a quid pro quo. You are generally predisposed to having research done on you including totally nonbeneficial research in exchange for the opportunity to get innovative therapy from the point

of view of the subject.

DR. TAMMINGA: I do not know that I would put it like that. Treatments for schizophrenia are generally very -- for most people with schizophrenia or at least for two-thirds or three-quarters are generally unsatisfactory. So it is not unusual for people to be dissatisfied with their treatment.

We try not to promise people that we are going to for sure be able to do something better. We are rather straight forward with them saying that we have the opportunity to try this, this and this or this given that you want that to be tried and it may be beneficial and it may not be beneficial.

MS. CHARO: Okay. But given -- I mean -- and here is the heart of the question. I will just be really clear about it. Given that people are coming with the hope that benefit might accrue to them personally, right, why does anybody in your experience -- what if anybody say, "Yes, your imaging research that has no beneficial to them?" Why don't any of these people ever say, "Sure, do this to me?" You mentioned some people might be looking for an opportunity actually to go for a washout. That was one possible reason people did it and I was curious what other reasons might lead people to undergo research that poses risks and does not have any apparent benefits from

the imaging itself?

DR. TAMMINGA: The washout is characteristically separate from the imaging so if somebody just wants to be drug free we have what is called the withdrawal protocol and they can consent to that. They do not have to consent to the imaging.

MS. CHARO: Okay. So this makes the question even clearer. Why would -- in your experience why does anybody say yes to enrolling in your imaging research?

DR. TAMMINGA: I have never really thought about it from that perspective for a lot of them do say yes. People with schizophrenia do not often times have a lot to do in their days and they do not have a lot that brings interest and challenge in their lives and they are not any different than you and me. They really like to understand things. They really like to make contributions to ongoing projects. They like to have -- they are curious about the scanner. They see the imaging pictures and they wonder what they mean. They wonder what those imaging pictures of their own brains would look like.

Those would be the reasons that come to mind that they would assent and say yes. We are very -- it is not therapeutic research so we do not --

MS. CHARO: Right. Well, I am trying to understand what the motivations are.

DR. TAMMINGA: They often times ask for --

MS. CHARO: To get a picture of what it is that is going on in people's own minds.

DR. TAMMINGA: They often times ask for pictures of their own brain.

MS. CHARO: Okay.

DR. CHILDRESS: This has been very helpful. Unfortunately, though, given the shortage of time, I have already told Henrietta to tell Harold that we will be running at least ten minutes over so we will not be starting the public testimony until close to 11:30. But I will need to bring this to a close and will you be able to stay around afterwards and sort of talk a bit to people as we are breaking up to grab some lunch?

DR. TAMMINGA: Sure.

DR. CHILDRESS: Because I think there will be some other things that people will want to raise and get clear on it. Anything you can provide in response to the questions that emerged and any other written material you think of would be most helpful. It has been a very illuminating discussion.

DR. TAMMINGA: I do have a paper, only one copy of a paper on drug-free research in schizophrenia that addresses some of the --

DR. CHILDRESS: Okay. If you could leave that

with us we will get copies made.

Dr. Sunderland, thank you very much and thank you for your patience.

DR. SUNDERLAND: It is my pleasure. I enjoyed it. Thanks for inviting me. It is an honor for me to be here. I have actually had the opportunity already to talk to Dr. Freeman earlier in the summer about some of the issues but not the imaging issues.

I thought I would come to you really with two simple points. One, as the chairman of the IRB at the NIMH where I have been for the last seven years, I have been the chairman for the last seven years, have been struggling with some of the issues you have on your table, and also the last 15 years I have been doing research with Alzheimer's disease and struggling with how do you do research with people who not will get cognitive impairment who may get cognitive impairment if you take them off drugs but who do have cognitive impairment by definition.

So I think the first thing I will do is just tell you a little bit as a researcher and as an academician. I cannot come anywhere without slides. So may I please show a couple of slides?

DR. CHILDRESS: That is fine.

(Slide.)

DR. SUNDERLAND: Great. Now it works.

Okay. The basic questions that we address at the IRB level, this is things that come -- sort of melds together both my IRB work and also I work with Alzheimer patients, is what is cognitive impairment. I am sure you have tried to address that as well. By definition we have a diagnostic and statistical manual. In psychiatry we have certain areas where cognitive impairment is defined by memory impairment as well as at least one other area of cognition such as judgment or vocabulary and visual and spacial impairments.

Who determines whether someone is cognitively impaired? This is incredibly important for us. It is usually the researcher at the NIMH and so there might be some bias here. So we have constituted a group of bioethicists. Dr. John Fletcher, who I think you already met with before, I think he was here earlier. He started that program and now it has been continued and doing wonderfully at the NIH and we often times borrow expertise with the Alzheimer patients by way of a consultant bioethicist.

What kind of person is cognitively impaired? Here I just wanted to make one quick point which is that any kind of person can be cognitively impaired and we have been focusing this morning on mentally impaired patients, particularly schizophrenic patients, but I want to remind

the audience that it could be a patient who has a heart attack who is under anesthesia. It could be a person who has got post-MI psychosis and we have to treat these people the same way we treat the psychiatric patients, the mentally impaired patients, otherwise I think we are guilty of impairing -- giving them a stigmatization which I think is very important. I would just like to emphasize that two or three times to you guys.

The issue of whether it is a state versus trait condition is something we always deal with. Is it temporary or is it permanent? With an Alzheimer's disease patient of course it is more permanent although gradual in onset. With a schizophrenic patient or with a patient in an MI situation in an ICU it would be a state or at least temporary reversal of their impairment.

Finally, who -- how can these cognitively impaired patients participate in research? We spent a long time trying to figure out how to do that. As to the issue of why they might do it I have a very simple answer as to why the people might do challenge studies and probe studies. Three very simple reasons. One, they get involved. These are people who are disenfranchised many times in the schizophrenic population. Certainly Alzheimer's patients are isolated at home. They have nothing to do. They feel worthless. And you give them

the opportunity to work with a group of enthusiastic people and they feel a sense of contribution again and it is a major benefit to them. This is not my words. This is their words over fifteen years hearing their reports back to me. They are thankful to us for being invited to be involved in research. Now that is something we have dampen somewhat because sometimes they will do things they perhaps should not be doing. So we are careful about that. So it is fun for them.

(Slide.)

Now just to give you a little data this is -- I brought a copy of a paper, two papers on informed consent in Alzheimer's disease patients, and we have used something that Dr. Fletcher developed which is a durable power of attorney. I am sure you all know about the concept. We are now applying it to research where we take people who are very mildly cognitively impaired at the very beginning of the time they work with us.

Here the mini-mental state is about 22. It is a very slight -- relatively slight impairment. People are still compos mentus in many ways but by the time we see them a couple of years later they are down to a 14 mini-mental. That is a very -- 30 is the highest score by the way. And that is the patients who are on the verge perhaps of going to nursing homes. So clearly they have

passed the threshold from being able to give informed consent and then no longer giving informed consent. I will show that visually in the next slide.

(Slide.)

In yellow is the first admission where we get an assigned durable power of attorney from our subjects. Usually it is a spouse. It might be a son or a daughter or even a friend and neighbor. They become their advocate if you will. And then by the time that we start studying them at this point where they still are able to give informed consent even though they are slightly impaired and may have an early diagnosis of dementia, by the time they reach the second time we see them two years later they are clearly very impaired.

We already have a seamless transition if you will between mild cognitive impairment where they are still able to give informed consent and major cognitive impairment where they can no longer of their own free will give informed consent although we very carefully -- it is not in the regulations yet but we use assent as a major component of the informed consent process much like we do with children so that if there is any physical manifestation of their unwillingness to work in our research program we withdraw them and that includes up to the very moment we do spinal taps or something like that.

MR. CAPRON: What does the GDS mean?

DR. SUNDERLAND: The GDS, excuse me, is the Global Deterioration Scale for Alzheimer's disease patients. So one and two is no dementia. Three to four is very mild dementia. Five, six and seven are very severe dementias, much more severe dementias. And seven, almost all sevens are in nursing homes by that time.

MR. CAPRON: Thank you.

DR. SUNDERLAND: There are no more slides.

Now in terms of -- we tried to develop this system along with Dr. Fletcher's advice and others because we felt it was important -- because we do a lot of imaging studies. I just brought a couple of pictures of what imaging studies, like we said, which is, you know, spend lots of money for a color picture basically, and this is a picture of an MRI here. This is the template that we use to analyze individual areas of interest and then we superimpose that template from someone's actual brain to a SPEC scan. This happens to be a SPEC scan. This is a minor version of a PET scan if you will.

We have used this to develop a therapeutic study. So I would go a little bit further than what Carol said. We think that PET scans can be used therapeutically as a dependent variable or a marker of improvement. We have shown that you can increase the colonergic binding in

some Alzheimer's patients given with a PET study. We are now using this as a rationale for giving them a certain new drug that has not been determined before. So this particular study that I am showing you, I have this data, led to a therapeutic study which has been introduced and we hope a direct benefit.

So our Alzheimer's patients we think can give us informed consent. Initially when they are mild and certainly if they give us a durable power of attorney -- thank you very much -- we think that they can give us informed consent via their advocates, the person they have chosen previously. We try to have everyone sign the papers at the beginning and at the end so as not to humiliate the patients by telling them today you can no longer sign this paper yourself. We ask -- even if it is just an "X" we have them put their name on the document so that we are not even sure who is giving us informed consent in some ways. Whether it is the DPA or the patient. We see them together as one uniform group.

The other important point I will make about that is that the DPA must be someone who knows the person before they become cognitively impaired so that they can go along with us in the research process so that they do not make a decision that is not congruent with what that patient would have done were they still cognitively

intact.

Now if I can shift a little bit to work with children because that was part of what I was asked to do today was to talk about imaging work. We have struggled with the issue -- I now have a hat on as an IRB chairman -- with how to do control studies with PETs in young people. And actually Dr. McCarthy was involved in an outside panel that we had. We convened about 20 people and I will leave this document with you if you wish, which is a review of this -- some of this meeting that we had. Whereas could we do more than minimally impaired, more than minimal research, minimal risk research with control subjects who were under the age of 18 and we came up with four answers.

One was tied to siblings of the impaired subjects, usually schizophrenic subjects, that they would be getting some direct benefit perhaps if, indeed, they were more at risk of developing the illness and secondly they were getting altruistic benefit by helping their ill sibling. We also talked about the issue of implicit pressure from family members to participate in that research and we addressed that issue.

I will not say we solved it but addressed it by having an outside panel of people review and meet with that individual or person before they made a decision to

go ahead and do the research. And then we also -- while the regulations do not specify the difference between young children and older children we shifted most of the burden of decision on to the older adolescent child if you will. We felt they were somewhat more able to give cognitive -- good informed consent for that particular issue.

And then finally the issue of voluntary radiation. Of course, PET scans or SPEC scans involve radiation. We felt that it fit under the CFR 46.406 rule that it was likely to yield generalizable knowledge about the subject's disorder or condition and then that gave us some rationale for the scientific risk/benefit ratio and why we might go ahead and allow a well sibling to participate in this kind of research.

So they were the two examples I wanted to give you but the theme I wanted to share with you was the theme of cognitive impairment, who is the person who has cognitive impairment, are they a medically impaired patient or a psychiatrically impaired patient? Is it temporary or is it permanent? And then finally is it something that a patient -- you can get around by looking very carefully at issues of assent as well as concept because too often I think in the IRB process we focus on concept and it is a static decision, a one time decision.

And from my perspective it is not. It is really an ongoing decision which is reinforced by assent every day of the ongoing protocol. And whether you need to emphasize that in your report I do not know but that is certainly how we are trying to.

Finally, in terms of education for investigators I would certainly agree with Carol that that has not been adequate up until now certainly with medical researchers and that is being addressed by the American Psychiatric Association now. They are developing a manual on informed consent which is being published by the APA and it is in press right now. A number of us have contributed chapters from our various specialties for that book and I think that will be a major tool that we use with researchers in the future.

DR. CHILDRESS: Thank you very much and thanks for packing all that under the pressure of time.

We will have about ten to fifteen minutes for discussion.

Let me just check in terms of the public testimony. Mr. Barker is here, right? Okay. We will start around 11:30 or 25 till.

Is Mr. Zohn here? Okay.

So we now will take questions and comments for Dr. Sunderland but also for Dr. Tamminga as well, and we

will involve both in discussion.

Comments?

MR. CAPRON: Yes, two questions. I would like to get an assessment from the IRB point of view of two points. One is the question that Alta Charo was raising with Dr. Tamminga which is the extent to which you have examined and thought about how to deal with this so-called therapeutic misconception that patients coming into a research unit to the extent that they are participating in a basic study of the mechanism of disease do not -- a study which was frankly described by Dr. Tamminga and I assume would be described by the IRB as one that does not involve direct benefit to them. In a position of having that therapeutic misconception because of their desperation to have some intervention that is helpful in a disease which may have been recalcitrant to treatment.

I guess I will just ask one question at a time. To what extent has this been something which the IRB has explicitly discussed and, if so, can you share with us what kinds of though processes you or your bioethics consultants have come to as to how that should be addressed as an issue if it is an issue?

DR. SUNDERLAND: I guess it boils down to the issue of a carrot. Is the carrot a therapeutic study where the quid pro quo is that you must first do the

challenge study? Is that the basic issue that you are addressing?

MR. CAPRON: Yes. It is, in part, that, yes.

DR. SUNDERLAND: Okay. I think each -- from the point of view of the IRB we address each protocol separately and they are not usually combined. A therapeutic study is not necessarily combined with a challenge study. So that we might actually address only the issue of a challenge study. So in some ways we are putting them -- putting the researchers at a greater disadvantage because they have nothing to offer the individual subject outside of the challenge study. They must prove to us that that is worthy in and of itself and is a stand alone study. So that we --

MR. CAPRON: Okay. I get that from the viewpoint of a committee looking at it and as I read the federal rules benefit the science can be weighed off against risk to the individual. It does not have to be benefit to the individual.

The question is whether you have examined systemically the position of the research subjects. Let me take a step back. We have heard from people who had been at the NIMH and have -- I came away with an impression -- and it may have been that we heard from unrepresentative people.

I came with the impression of people who basically were being asked to make a commitment to come and be subjects for a period of time, maybe an indefinite period of time, but they were not typically coming on so as to go into one study but really were sort of saying, "I have a mental problem. The hospital I have been at has not been able to deal with it and I am being referred down here because NIMH is a source of hope for me."

When they get here and what is contemplated is that they will be an inpatient at the clinical center -- is that where your research is done?

DR. SUNDERLAND: Yes, it is.

MR. CAPRON: -- for a period of time that may be months, maybe even more than months, into years.

DR. SUNDERLAND: Right.

MR. CAPRON: Now in that setting the person's -- the inducement was upfront with the hope that they would come in. Have you given thought to how that would affect their agreement to be in a particular study?

DR. SUNDERLAND: I am actually familiar with the specific example that you have been faced with, with the 3 West questions and Dr. Post and some of the issues.

MR. CAPRON: Okay.

DR. SUNDERLAND: So I know the details. In fact, I have been involved with Dr. Calgary in writing a

response to some of those issues.

As an IRB we were aware that there were subjects who were staying a long time. What we were not aware of is that people were presented with multiple protocols at the same time. And we are making changes to make sure that is not --

MR. CAPRON: That is -- I am glad to have a follow up on that.

DR. SUNDERLAND: Yes.

MR. CAPRON: But what I am concerned about is I think Professor Charo was putting her finger on an example of the potential in this setting for therapeutic misconception to operate, not simply because of the quid pro quo.

DR. SUNDERLAND: Right.

MR. CAPRON: But just a sense that, gee, you are doctors, you are offering me participation in something, it has got to be good for me at some level, otherwise I would not be offered it, and I am in a situation where I have entrusted myself to you. I have come into this institution on some kind of a long-term involvement. And to echo something Harold Shapiro said, none of this is a question about the motives of the individual research. It is not impugning anyone.

I am asking you as the outside group looking

at it, who obviously you have set up, you have showed us, you think about these questions, I wonder is this a question you have thought about and even now or have you written it up, do you have a consultant's paper? Have you addressed it in a way that could help our discussion more than the few minutes that we have to talk about it even?

DR. SUNDERLAND: Quickly, no, we have not written on this.

MR. CAPRON: Okay.

DR. SUNDERLAND: We have tried to address it. I do not know the best answer for you. We are struggling with this issue as an IRB as to how to present. I do work as a clinician as well as a researcher and I am struck by the similarity between that very issue when you do an individual patient in your private office as opposed to in a research center. It is not so different from when a patient walks into your office. They have come to you with the idea that you are going to help them.

DR. TAMMINGA: That is right.

DR. SUNDERLAND: And no matter what you say to them, whether it be this may not work, or while I can give -- I will tell you the research study that showed 90 percent of the time it will work, it may not work for you. So really you are doing an individual research project with that one person in your office privately. I do not

think it is so different in a research setting. No matter what you say the people come to you with an idea that you will cure them even if you say this is not going to be a therapeutic study. It may help understand -- help us understand science better and you will be making a major contribution but I can guarantee you for our Alzheimer's patients that is a benefit. They see that as a tremendous benefit.

MR. CAPRON: But there has been -- but I would wonder if you have an institution where this is going on whether this is an empirical question. I mean, you could ask people retrospectively as a part of an exit process or as well as part of an entrance process whether you were asked to participate in the studies that you were asked, at that time did you expect to receive some benefit from it? It would be interesting if a lot of people said, "No," and then we are over on the quid pro quo side, which may be fine.

It is not an undue inducement. The inducement that I get something from being here. I am in a bad state. You offer a nice hospital with the best quality care there is in the country for these problems and I am willing to give you some time on your research studies as long as you are not going to kill me. That is a quid pro quo and that may be fine.

But that is different than a person saying, "Well, sure, yes, I thought I would benefit from participation in the study." If you saw that a lot then I would say institutionally you have some obligation to address it and we as an institution have an obligation to think about how it might be addressed not just at NIMH.

DR. SUNDERLAND: I totally agree with you.

MR. CAPRON: But you have not done those studies?

DR. SUNDERLAND: No, those studies have not been done and I think the sensitivity of the medical researcher is not towards those questions up until now. I think we are beginning to shift our focus a little bit.

Around the issue of genetics testing where there is a potential predictive importance to genetics testing we are beginning to ask people ahead of time do you want to know the information and what does it mean to you to hear about this information. Would you want anyone else to have this information available? Do you want us to do further tests once we -- as we can store people's data for many, many years.

MR. CAPRON: Right.

DR. SUNDERLAND: So we are beginning to proactively address this question and I do not think we have in the past adequately.

MS. CHARO: Can I follow up just on exactly that point, please, because on our IRB it is most common in the consent forms to tell people that their decision to withdraw from the research will not affect their healthcare in any other way and yet that promise could not be made on your research ward, for example, because somebody who consistently failed to complete their research protocols or consistently refused to participate you said would be transferred off to a nonresearch ward, right?

DR. TAMMINGA: Yes. Not without treatment though. I mean, we would not just take them from a drug-free state and transfer them off to another ward.

MS. CHARO: I understand that. But their access -- see, this is basically what I was saying. If people are entering these situations because they see it as an avenue to innovative therapy, that is how they -- in their minds it might be -- it is going to be innovative therapy, an alternative to what has not been working for them.

And then persistent refusal or change of mind about participation is going to mean that they will be moved back to standard therapy options that are available on a nonresearch ward. It is very much a change in their healthcare from their point of view because the innovative

therapy that is found on the research ward from the point of view of the person coming in is healthcare, not research.

Am I making any sense?

DR. TAMMINGA: Well, I think the innovative therapy is the research.

MS. CHARO: That is my point. So the point of view of the subject is it is not research. That is care. And some of the other little things may be research but that is -- this is the essence of the therapeutic misconception. The point of view is crucial in the characterization of what is going on. It is --

DR. CASSELL: It is not a misconception.

MS. CHARO: Yes.

(Laughter.)

DR. CHILDRESS: Okay. Diane, Eric and Trish.

DR. CASSELL: What about --

DR. CHILDRESS: Oh, you had a second one. Sorry.

MR. CAPRON: The second one with these challenge studies, again to the outsider they look so disturbing. How do you evaluate whether or not you are going to allow one of them to go on? Again if this is a question to which you have given the kind of thought that resulted in guidelines or elaborations and you prefer to

share that in writing with us, we have limited time, I would be happy to have it.

But where you have mentally ill patients who are on treatment and the study is going to take them off and then give them ketamine or something and induce psychosis and memory impairment and so forth in them. How do you decide which of those studies are acceptable and which are not?

DR. SUNDERLAND: Well, there are -- I will give you a quick rule of thumb and then also refer you to a paper that I will send to Dr. Childress if you like written by two of our IRB members, Frank Miller and Don Rosenstein, where they address the issue of challenge studies. So let me address --

DR. CHILDRESS: And that one we actually have. Thank you.

DR. SUNDERLAND: You have it already. Okay, fine. So you have that paper.

The rule of thumb that we use is that one that we are extra especially careful about the review of the informed consent at several points during that study and secondly that we are not exacerbating the symptoms beyond what the patients have fully experienced in the past. So we are not giving them new symptoms that they are unfamiliar with. So that if we are going to -- and we use

that as a threshold marker.

So if the schizophrenia patient is to take ketamine where there are such studies they have to understand they might get some of the symptoms that they have experienced previously. Rarely would they ever get a symptom that they have not had before and we go over that with them at a time when they are fully able to give informed consent.

MR. CAPRON: Is there a documentation of the long-term risk that -- having reintroduced these symptoms it will be harder to get back or is that not thought to be a long-term risk?

DR. SUNDERLAND: I cannot speak to the schizophrenia literature. I do not know that as well. But for Alzheimer's disease we give a drug called scopolamine (?) which causes memory impairment. And we can -- we have shown over and over again that the impairment reverts back to their normal baseline within four to six hours and that there is no evidence of it 24 hours, four months or six months later. But they still progress but there is no evidence of an acute exacerbation from that immediate psychopharmacologic challenge.

MR. CAPRON: But as chairman of the IRB that reviews these you do not know the answer to the question on whether or not in schizophrenia inducing it could have

any long-term consequences?

DR. SUNDERLAND: No, no, I do know as chairman of the IRB that they do not have long-term effects. I have not studied it myself personally so I cannot tell you that --

MR. CAPRON: So you say there are papers?

DR. SUNDERLAND: Oh, yes, there are papers that have shown that these drugs are acute -- rather short acting drugs and there is no reason to understand that they would think that they would have chronic effects.

MS. FLYNN: If I could just add there is considerable literature actually that looks at the effect of relapse and in a typical person with schizophrenia who may experience two to four episodes of psychosis a year if they are untreated their psychotic episode may go on for weeks and repeated relapses over a period of years will produce permanent disability. These studies, and again I am as uncomfortable as many are with them, but these studies typically involve exacerbation of symptoms for a matter of hours, which is much less than what, you know, an ordinary course of illness would see and what many people with this disorder have experienced repeatedly.

DR. TAMMINGA: I could add a bit on to what Dr. Sunderland says in terms of telling you what I had to

go through with my IRB in order to do these ketamine studies.

Initially we were allowed to do two patients. We knew that ketamine was very short acting and has a half life of 20 minutes and we knew that the amount of psychosis exacerbation was rather small and after we did two patients we had to report back to the committee. For all of the patients that we -- and then when we did six people we had to report back to the committee and tell them what happened.

We had to quantify things for them. We had to quantify that there was actually about a 25 percent exacerbation of symptoms. So compared to the 100 percent symptoms that they have in their drug-free state they had about a 25 percent exacerbation and it lasted for 20 minutes and in the very long follow-up that we had because they remained hospitalized for months there were never any chronic sequelae. But our IRB now requires that if there is a provocation of symptoms that it is mild and short lasting and that there are no long term sequelae. We have to document that.

MR. CAPRON: And you document that?

DR. SUNDERLAND: Yes.

MR. CAPRON: And you would typically report that documentation as part of your process?

DR. TAMMINGA: Yes.

DR. SUNDERLAND: Oh, yes.

DR. TAMMINGA: Every six months. In the ketamine cases we were more restricted than that.

DR. SUNDERLAND: We did the same thing at the NIH. We did it every three patients. Now we have a huge paucity of biologic tests in the mental health field in general. And doing a challenge or a probe test like this with ketamine is not so different than giving a diabetic patient an insulin tolerance test.

DR. CASSELL: Of course, it is.

DR. SUNDERLAND: No, I am sorry, it is not.

DR. CASSELL: Of course, it is. Now I will tell you something, when you give somebody with diabetes a challenge by either stopping their insulin, you do not give them an idea of their state of being.

DR. SUNDERLAND: We need to have --

DR. CASSELL: When you do that with -- excuse me, please.

DR. SUNDERLAND: Yes.

DR. CASSELL: Give it a chance. When you do that with ketamine you are telling somebody about their state of being. It is considerably different. It is like talking about long-term effects. One of the long-term effects of anything is the memory that it happened. And

that does not produce hallucinations and so forth but it changes a state of themselves. So if you are naive enough to believe that a ketamine challenge and stopping somebody's insulin for a couple of days are the same that in itself is an interesting thought.

DR. SUNDERLAND: I think the point I was making is not that there are no differences but that we need to have biologic tests in the field of mental health to go beyond the idea that these are -- to go beyond the stigmatization of these medical conditions. Schizophrenia, while we do not know much about the biology of the illness yet, we do need to develop these tests so we can understand the brain chemistry.

This is the small beginning so that from the point of view of an IRB I think we have to take very cautious steps in this direction so that we can develop tests that are medically acceptable so that we can go on into the 21st Century in this field which is otherwise stuck 30 or 40 years behind much -- the rest of medicine. That is my point. Not that they are not -- they are not exactly analogous but they are in the same ball park. We are trying to develop -- researchers around the world are trying to develop small steps in the way of biology testing.

DR. CASSELL: Well, I have a turn coming up so

I will --

DR. CHILDRESS: Okay. Let me tell you the turn is going to be limited to 30 seconds to each of you because we do have to have public testimony and then we have to break.

Okay. Diane, Eric and Trish, 30 seconds only.

DR. SCOTT-JONES: Okay. I will speak very, very quickly. My question is about assent. You emphasized assent and could you just say a little bit about the manner in which you do that by giving an example?

DR. SUNDERLAND: Certainly. As a researcher individually with an Alzheimer's patient every time we do a procedure we actually -- if that procedure has been covered by the overall protocol we will review it with the patient the night before and the morning of, and ask if they want to go ahead. That is particularly important with the dementia patient because they forget having signed anything weeks or months or even days ahead of time.

So we will go over the final tap which is perhaps the most provocative one for the individual and the most difficult for the family to accept before and then the morning of. If they show physically or verbally any reticence then we will hold off the procedure. We may

address it with them later but we will stop it that day.

DR. SCOTT-JONES: Okay. You post-pone. You do not allow them to discontinue.

DR. SUNDERLAND: We post-pone and then offer it again. If they decide a second time not to do it then we discontinue it entirely.

DR. SCOTT-JONES: You only try it twice?

DR. SUNDERLAND: That is correct.

DR. SCOTT-JONES: And do you know the percentage of declines at the point of asking assent of someone for whom you have informed consent?

DR. SUNDERLAND: I do not have it at my fingertips but it is less than --

DR. SCOTT-JONES: Or ball park.

DR. SUNDERLAND: It is less than 15 percent of our subjects decline.

DR. CHILDRESS: If you could provide any information that would be helpful for us.

DR. SUNDERLAND: Okay. I will see if I can do that.

DR. CHILDRESS: All right. Eric, 30 seconds and, Trish, 30 seconds because we need to go to public testimony.

DR. CASSELL: I have two comments. One is did the two patients who were the beginning of the ketamine

challenge, whether they were the two patients who would go first to find out if it had long-term effects, did they know that?

DR. TAMMINGA: Yes. They knew it and the families knew it.

DR. CASSELL: Fine. Secondly, we understand the need to develop biological tests otherwise there would be no need to protect human subjects and my -- when I hear you I do not have to ask the other question I was going to ask. Of course, you want to have a biological test. Who does not want to have a biological test. It is not that. That is not the issue at all. It is what is the price of that biological test? That is what -- that is what this thing is all about. What is the price? What is the human price of that benefit?

DR. TAMMINGA: Can I say a short thing about ketamine a minute that would speak to at least some of your comments? Ketamine is a drug that will mildly exacerbate one or two psychotic symptoms in a person. I do not know that I generally think that the state of being of a schizophrenic person is really defined by those psychotic symptoms. A schizophrenic may hear voices and that may last for ten minutes but it is not like they become diffusely -- that their mind becomes diffusely taken over by something.

DR. CASSELL: Just to clarify. If you had a panic attack, even one panic attack, and maybe if it lasted an hour, it will never leave your mind that you had it.

DR. TAMMINGA: That is for sure. That is for sure.

DR. SUNDERLAND: I mean, I -- my point in making the reference to medical tests is -- let me give another analogy that might not -- that might be more acceptable. Which is the idea of someone who has a heart condition. When they go in and they have an appointment with their doctor six months from now and they start to worry about the fact that they are going to get another stress test when they go to that cardiologist's office. Three months later they are worried about it again because they know their symptoms might be exacerbated and they might be precipitated by that treadmill test they are about to have or by the infusion.

I do not think that is necessarily very nice for them. It is very psychologically damaging. The one thing they are worried about is a sudden death that might happen in the doctor's office. We have not studied that.

So to me we have not studied the implications, the long-term implications of that kind of situation either. And I would say that the psychiatric patient is

not so different. Yes, it will be psychologically difficult for them but it can be handled if done so properly. And much like the cardiologist should be very careful psychologically when their patient when they come in for a treadmill test. That is really what my point would be.

DR. CHILDRESS: Trish, 30 seconds, and then we go to public testimony.

MS. BACKLAR: My question is how do you -- again like my question to Carol, how do you transition out your patients? But I want to back up what Eric is saying. I personally am very concerned about the discomfort and the psychological discomfort of these kinds of research and challenge issues. But how do you transition out your patients?

DR. SUNDERLAND: Transition them out from --

MS. BACKLAR: From the basic --

DR. SUNDERLAND: -- from clinical research --

MS. BACKLAR: Yes.

DR. SUNDERLAND: In our case it is a little bit different. The Alzheimer's patients, they are all referred to us by primary physicians. We do not want to be in a situation where we maintain the care for the individual. So they must be referred by an individual ongoing doctor who gives us their referral and we refer

them back to that doctor. Or help transition them if it is time for them to go into a nursing home. We might help that process. But it is via their local doctor. So that is not -- we do not take on the responsibility of the primary physician for just that reason.

MS. BACKLAR: And your schizophrenic patients, the people with schizophrenia, their transition --

DR. SUNDERLAND: From the institute -- the IRB -- we do not have a requirement of that at the IRB level so I cannot speak. From the IRB point of view we do not have an actual requirement of the transition.

MS. BACKLAR: All right.

DR. SUNDERLAND: But I know from clinical practice --

MS. BACKLAR: That is important that you know.

DR. SUNDERLAND: Yes. From the clinical practice my understanding is that most of the referrals are also doctor to doctor in the institute but I would have to check on that.

DR. CHILDRESS: We thank you both very, very much for being with us, for sharing these thoughts, and also for sharing materials with us. If you could pass those on and Henrietta or Pat could get the materials from you, we will be glad to make copies and distribute them. If you can think of anything else that might be useful to

us, we would welcome that.

If you are around for a few minutes after we have public testimony then perhaps there may be other individual questions.

I have one person who is planning to present public testimony, Mr. Allan Barker.

Mr. Barker, we appreciate your coming and we do limit public testimony to five minutes. So you have -- if you can come and sit at the table or stand and use the microphone there or sit there beside Dr. Sunderland would be fine. If you have some written testimony we would very much appreciate a copy of that which we could also distribute to the whole commission.

MR. BARKER: I have already given it.

DR. CHILDRESS: Okay. Thank you.

STATEMENTS BY THE PUBLIC

MR. BARKER: I am here to talk about electromagnetic antipersonnel weapon and mind control technology. While there is still denials that such weapons exist anyone who is remotely familiar with the technology and its history can only conclude that the United States has such devices.

Dr. Robert Becker wrote in his 1985 book The Body Electric that we would have to be very naive to assume the United States has no electromagnetic weapons.

Microwave beams can be modulated with voice signals such that when the beam is directed towards a subject's head he hears a voice. This has been reported in the open scientific literature since at least 1975. There are U.S. patents for devices with microphones which will project a speaker's voice into a subject's head.

In addition to voice projection microwaves can impair performance, affect heart rhythms and cause bone damage due to heating effects.

MS. BACKLAR: I cannot hear.

DR. CHILDRESS: Excuse me, sir. Sorry, Mr. Barker.

MR. BARKER: This is just the hardware. How this technology is used can be likened to the software. For example, when combined with familiar surveillance devices such as miniature pinhole cameras microwave weapons and other so-called nonlethal weapons can be used to reversibly condition and train people inside their own homes. They may not even be aware this is going on.

Because the effects of these weapons mimic the symptoms of some mental illnesses and can cause brain damage in addition to the dramatic stress of torture the victims typically have no where to turn. They may be further abused by the mental health system.

The CIA admitted in Appendix E of the Interim

Report of the Advisory Committee on Human Radiation Experiments that it investigated the use and effect of microwaves on humans. It determined that this research was outside the purview of the Radiation Committee. I hope it will fall within the purview of this committee.

Beyond microwave technology I want to talk about implanted devices. Their existence is often denied. Implanted devices, even brain implants, have been around for years. There are U.S. patents for implantable tracking devices that allow people to be tracked from cellular phone towers. Implanted listening devices and even EEG analysis devices are well within the capability of black budget projects.

As recorded in December of 1993 by the City Sun newspaper of Brooklyn Brian Wrung (?) discovered after being released from a correctional facility that he had various devices implanted in his body. These devices showed up on CT and MRI scans. Even so he had difficulty getting a lawyer to represent him. Surgeons citing fears of reprisal would not remove the devices from his body. The group of Physicians for Human Rights refused to assist him or help him find a surgeon.

Major newspapers did not cover the story. This last fact should not be a surprise. According to the Columbia Journalism Review the data on human radiation

experiments that was reported as new in 1993 had actually been known for almost a decade. A congressional committee had issued a report detailing those abuses in 1986. The report was widely ignored and misreported.

The indifference shown towards still surviving victims of these experiments is shocking. I have personally experienced harassment and torture inflicted by people using mind control or influencing technology. It began when I was doing research work associated with the intelligence community. In the bizarre logic of this sort of harassment those who claim to have experienced it firsthand are often accorded less credibility than those who have not. I do not let this stop me from trying to describe how truly horrifying it is to have your very mind repeatedly violated inside your own home where there is no escape.

Just describing the hardware capability does not begin to touch on the software techniques of psychological warfare that are applied using the technology. I hope this committee can begin to address some of these human rights abuses. But people who commit such crimes will think nothing of lying or worse to cover up their involvement.

What would be worse than involuntary human experiments like these would be if the techniques become

standard practice to be applied regularly and in secret. Thank you.

DR. CHILDRESS: Thank you, Mr. Barker. I thank you for your patience this morning as we ran so far behind.

Are there any questions for Mr. Barker? Any comments?

DR. DUMAS: Do we have copies of this one?

DR. CHILDRESS: Yes. You say copies have been provided?

MR. BARKER: Yes.

DR. CHILDRESS: Copies have been provided so that we can make copies.

DR. _____: He just brought one in this morning.

DR. DUMAS: Oh, okay.

DR. CHILDRESS: Okay. So we will get copies made.

Any other questions or comments?

Thank you very much, Mr. Barker.

Committee, let's get some lunch. Dr. Shapiro, be back here immediately.

DR. SHAPIRO: Immediately, yes, meaning that we would like to get the joint session started.

(Whereupon, a luncheon recess was taken at

11:52 a.m.)

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

1:35 p.m.)

FEDERAL OVERSIGHT OF RESEARCH INVOLVING HUMAN SUBJECTS

DR. CHILDRESS: We are very glad to have this afternoon session devoted to an issue that Alex Capron raised on the placement of OPRR forum or OPRR-like structure within the Federal Government. We are also getting a third paper by Tina Gonzalez that will deal with the possibility of a regulation of private research as well.

But for this afternoon we are dealing really with oversight of federally conducted or funded research and w are very glad to have Charles McCarthy, former head of OPRR, National Commission of Ethics, and John Fletcher, a former director of Clinical Ethics, NIH, and most recently the Center for Bioethics, University of Virginia, both of whom presented papers, be with us this afternoon. Each will speak about five minutes and then Alex Capron will raise questions but before then we will have a --

(Laughter.)

DR. CASSELL: I speak not only for myself but when we joined together just now interesting things are happening in the other group, ongoing interesting things, and we are not -- we do not really know enough about them as they are going on. So I do not know how to solve that

problem but maybe they feel the same way or should.

(Laughter.)

DR. CASSELL: I just wanted to raise that point and I have finished my 28 seconds.

DR. CHILDRESS: Okay. Actually I think it was raised in the previous session and I think that there will be an effort to deal with that and try to balance those two for the January and February meetings as I understand it. But thanks. All right.

DR. CASSELL: I am sorry.

DR. CHILDRESS: Charlie and John, you have provided such fine papers for us. Each, if you would like, to just say a few words at the beginning, no more than five minutes to open it up. Anything you would like to highlight. Charlie can go first and then John, and then Alex will kick off our discussion with you.

DR. McCARTHY: Thank you very much and I am delighted to be here. I want to wish this commission all the best. We have hoped for its existence for many, many years. We are delighted with the make up of the commission and mandate, and so we hope that you will have great success in fulfilling what I think is an extraordinarily public function.

As you know, I retired from the government about five years ago and I have recently reminded my

friends at FDA that the government has degenerated dramatically since I left.

(Laughter.)

I reminded FDA that they have now approved Ex Lax or they have banned Ex Lax and approved thalidomide.

(Laughter.)

And what further evidence could anybody have of the decline of the government?

What I want to say to you today is something about the organization of OPRR. First, I think you need to get a very, very quick understanding of where it is now. Namely that although the authority for OPRR is set in the law and directed to the Secretary it is delegated down through the Assistant Secretary for Health, through the Director of NIH, and finally to the Director of OPRR. So there are several channels above OPRR that feel that they have some right or some authority and responsibility for the protection of human subjects.

Usually this comes up when there is a disagreement and so it is quite possible for there to be more than one cook stirring the soup or putting ingredients into the soup at the same time.

I found that that ambiguity as to who is really in charge cut both ways. Sometimes it complicated our lives and sometimes it actually hindered OPRR from

doing its work. At other times we found champions. For instance, there were times when the Director, NIH, was very unsympathetic to the work of OPRR. In that case we often turned to the Assistant Secretary for Health for backing in a particular case. In some cases, particularly with Secretary Califano, we found he was willing to back the decision of OPRR and so we identified ourselves as a secretarial office.

So, in fact, we had stationery in our office from the Secretary's office, from the PHS level and from the NIH and we chose the stationary according to the situation. And we found that the very ambiguity sometimes hindered us and sometimes helped us in getting our work done.

So I just want you to know I had a boss who one time said to me, "The bureaucracy is like a 12 string lyre. It is extraordinarily difficult to play and some people only squeak and squawk. But those who learn to master the instrument can make beautiful music."

What I am suggesting is that no matter what you do there will always be that bureaucratic mastery that must be developed and it is that that you cannot put into laws or regulations or even into your reports. Yet it is that that will ultimately either make OPRR succeed or fail. So I think it is important to keep that in context.

One other comment I wish to make and then I will talk a little about my findings, and that is simply that OPRR is the kind of office that looks at haystacks and it searches out needles. As a consequence an enormous amount of what OPRR does turns out to be a deadend, a negative finding and nothing was wrong, nobody did anything bad, we just had to check.

Now and again it finds a needle. So what OPRR is known for in the public world are those few needles it finds that OPRR feels in the day-to-day work of the office is the enormous burden of that haystack. Consequently it is difficult to recruit and to retain highly competent well-motivated staff. Sometimes they may get so numb looking at the haystack that even when they run across a needle they are not sensitive to it.

Again I think no matter where the office is placed that kind of problem will persist and I think it is very important work that must be done but remember you are dealing with those rare exceptions first of controversial cases and, secondly, bad judgments by OPRR, or an IRB, or by an investigator, or by an institution, or all of the above, and those must be dealt with promptly and expeditiously. But they first must be identified and that can only be done in my judgment through a sound educational program.

So the points I simply want to make are first and foremost that even as you heard today the discussion about minimal risk and other kinds of issues none of that can ever be fully captured in a regulation. It always must be amplified by education to raise sensitivity or the regulations themselves will not work. You may change the wording. You may redefine the risks. You may redefine benefits, whatever you wish to do, but unless that is accompanied by a strong and continuing education effort it will finally become fossilized and it will have just the opposite effect that you would like to intend.

So that education program must be alive. It is hard to find people today who read the reports of the old National Commission. They were dynamic at the time but now they are gathering dust from the shelves and your reports in time will have the same fate. As a consequence unless that education program is renewed, updated, and continuous, I think no placement of OPRR or staffing or other kinds of bureaucratic efforts will ever be fully successful.

There also, of course, must be a compliance dimension but I think that is self-evident. OPRR, no matter how big it is, or how good its staff is, must be always draw on outside expertise. It deals with all kinds of research in all kinds of disciplines. And often times

a factual situation requires a good deal of understanding.

You spent quite a lot of time this morning talking simply about washout studies and those imaging studies simply trying to learn what the scientist is trying to do and how it is to be done. Only then can -- if you understand the process can you then begin to wrestle with the ethical issues. And OPRR cannot possibly have all that kind of expertise and, therefore, I would argue that it needs to be in a position to command that expertise particularly from the intramural scientists within the department but also from outside if that expertise is not available inside.

On occasion OPRR's work overlaps with other ethical offices. Many times the animal issues and the human subjects issues get intertwined. On occasion the research issues relating scientific conduct or misconduct get intertwined with human subjects issues. Therefore, I think it must always be in close alignment with those other offices that have a cooperative relationship with them so that when an investigation or a compliance issue arises there is already an easy relationship across those offices willing to work together.

So that brings me then to the set of conclusions that I would like to make. The first is I think that at times because of congressional pressure,

White House pressure, pressure from the Office of Management and Budget, pressure from powerful institutions in the country, major universities and the like, I think OPRR if it is to survive and to thrive must have the backing of a cabinet level officer. Therefore, I would like to see the office established in the Office of the Secretary but because that office itself is highly politically motivated I think it should be protected by some additional kinds of legislation that would keep the Secretary even from interfering unduly in the work of OPRR.

I would like that office to be filled not by a political appointee but by a career person with proper qualifications. I would like that person to have the level of an Undersecretary which is sufficient, I think, in virtually every case to exercise supervision over the various agencies within the department and give sufficient stature so that person could have some weight in the interface with other agencies across the Federal Government.

I think it should be located in a larger ethics office in the Secretary's office so that the sister offices on animal care and humane care and use of laboratory animals and the ethics of research integrity are closely aligned and can easily interact whenever that

is appropriate. I think it must always have an education branch and that must be funded.

Then finally even OPRR independent as I would like it to be needs to be accountable to someone. So I would like to see it accountable to a particular set of committees in the Congress reporting no less than annually, reporting on the performance of the various agencies within the Department of Health and Human Services, reporting on the performance of the other agencies across the Federal Government, and giving an account of its own stewardship.

Those are the main kinds of recommendations I would make and I think OPRR then with the proper personnel and the proper training of that personnel could serve an even more important role in the future than it has in the past.

DR. CHILDRESS: Thanks, Charlie.

John?

DR. FLETCHER: Mr. Chairman and members of the commission, thank you very much for inviting me. It has been a real pleasure for me to engage in this project, in this paper. I have had a number of interesting interviews and visits. My findings revolve around a central problem that I think is irremediable without a more radical solution than Dr. McCarthy recommends.

The problem is that OPRR's location within the National Institutes of Health is a very imposing conflict of missions. The two agencies have different missions. OPRR's mission is to uphold the primacy of respect for human subjects. NIH's mission is as the nation's main sponsor, federal sponsor, of biomedical research. And this -- the location of OPRR within the NIH, the fact that its staff is supervised by the Deputy Director of Extramural Research, is a conflict of missions that does create conflicts of interest.

Dr. McCarthy's report, interestingly, detailed one very significant conflict of interest which he adroitly negotiated his way around when Dr. Healy asked for a briefing on the Gallo investigation and she got one from the Office of Scientific Integrity for which she was criticized and they were criticized. Dr. McCarthy negotiated his way out of that recognizing that that would have been an extremely sensitive and palpable conflict of interest. But the fact that the request was made shows you the tip of an iceberg, which I have had the privilege of investigating in more detail, which is filled with examples of conflict of interest.

The most compelling proof to me of the problem of OPRR's location is if you compare the record that OPRR has of investigating violations in PHS agencies, that is

the NIH, the CDC and to a very small extent in the FDA, the first two agencies, the time required for those agencies to make correction, when you compare it with the track record of major universities in making quite similar changes, it is -- it cannot be explained in terms of complexity. It can only be explained in terms of the ingrained attitude of administrators and veteran scientists within these agencies towards the OPRR.

The tools that the OPRR has for its normal every day work with its -- with sources of its assurance, namely the threat of removing -- the threat of suspension of federal funding, the threat of bad publicity, et cetera, et cetera, these tools do not work when it comes to the agencies of the Federal Government. They are not worried about their funding.

And my -- in my own professional opinion they look down on the OPRR. There is a lot of data about the lack of respect of OPRR. But the data is in the -- the main data is in the time that is required to make changes.

I feel fairly confident on this point that there is a very imposing problem. The solution that I recommended follows the example of the Nuclear Regulatory Commission which was at one time part of the Atomic Energy Commission and which had very serious similar problems. The Office of Government Ethics was at one time part of

the Office of Personnel Management and they had similar problems of being overshadowed and running into problems of conflicts of mission which escalate into conflicts of interest.

Both of these agencies today are independent. They are located in the -- broadly speaking in the executive sector. They report to Congress. They are very well funded. The Office of Government Ethics is extremely well funded and has an outstanding education program.

So I recommended in conclusion that the commission consider cutting the Gordian knot of conflicts of mission which lead to conflicts of interest and recommending that OPRR have an independent location that is certainly accountable to Congress, which will be responsible for funding it, but reporting to the President as a matter of accountability.

That there be created a new national office for human subjects research with a view towards a mission which I think is compatible with the commission's previous statements about universalizing protections of human subjects beyond the federal dollar. Our federal policy today follows the dollar and this is morally and legally questionable. All research subjects in the United States deserve equal protection of IRB review and informed consent. The new office of human subjects research ought

to have that universal mission along with being the primary agency responsible for monitoring the quality of compliance with the Common Rule.

I also recommended that there be a national advisory committee for human subjects research to be appointed within the context of OPRR for purposes of ongoing policy debate, ongoing debate about interpretation of the regulations, a forum for significant problem cases. I recommended that this not be set up according to a commission model but as an advisory committee to the new national office to meet at least four times a year under the national advisory committee act and so forth.

The national advisory committee, I believe, would partially meet the longstanding recommendations of Professor Katz and others. It is not the model that he proposed but it goes partially towards meeting the need for a permanent national forum and a source of expert advice.

Before I conclude, Mr. Chairman, I just remind the commission that the -- my attachment number one which shows that OPRR is 12 levels down in the bureaucracy at the NIH, my understanding would be that any recommendations that the commission might make which would become OPRR's responsibility would find these recommendations would quickly find themselves in this

lower realm of problem and be in effect asking for the same kind of trouble that affects OPRR on a -- not just on a periodic basis but on a permanent basis.

So if you want to help yourselves to be free from this problem I call upon you to work together to find the ways, including the political ways, to liberate OPRR from its present problems and make it an independent agency with sufficient stature and tools and staff to do its job.

Thank you very much.

DR. CHILDRESS: Thank you, John.

I have asked Alex to kick our discussion off. I know Alta has a comment to add too.

MR. CAPRON: I want to thank our paper writers for two really very well put together and illuminating papers, both analytically and in terms of their content adding to our knowledge of the history both by looking at sources and bringing them together and since each of these paper writers has a great deal of personal experience adding to the record by bringing out things which I do not think have been on the record before, there is a great deal of benefit we get by having turned to Drs. McCarthy and Fletcher. The wisdom that is borne of their experiences is very apparent in what they have written.

Since we began this topic by thinking we would

look for opposing views it is clear that the conclusion to which they come does differ in some ways. What is most remarkable to me is the convergence and congruence of the two papers not only in their description of what has happened but their diagnosis of the meaning of that. If not in their proscription of how to respond there is a surprising amount of congruence.

There are certain parts of the papers, which while interesting, I do not think we have to be as directly concerned about. Obviously Dr. McCarthy speaking out of his personal experience necessarily provides an endorsement of the methodology that the office that he headed has used and he gives good argument for why that methodology is to be preferred. But I do not think that the question of the methodology necessarily affects the location, which is the issue that we are mostly addressing.

I think it would be incumbent on either anyone running the present office in its present form or any office of this to learn from Dr. McCarthy's comments which I think are generally very well taken but it is not directly on point to the issue. Likewise, Professor Fletcher's philosophical standpoint, which I personally share, on the relative balance between the imperative to do research and the imperative to protect human rights is

interesting but I think actually we could extract that also from the paper and his actual recommendations would not differ. So in each case I hope that we do not really focus on those and if people disagree on that I hope we can put that aside.

The papers together present a picture of gradual expansion of the oversight function punctuated by crises and scandals, some that were widely known and some that through great manueverings were prevented from becoming very public scandals. Sometimes the responses seem to be aimed at the highest level of human subjects protection.

They were motivated by a recognition that there was a problem and a need to respond by increasing the level of protection. Sometimes it appears that they were motivated by institutional impulse towards self-preservation and both in resisting rules sometimes but also even in endorsing greater oversight as the way to avoid an outside interference. A strategic retreat on a point to save -- to win the war while losing the battle.

The central issues that come out of both papers are the lack of perceived authority outside of the NIH for the agency which those of us from outside recognize as the major agency in the government, although we are reminded by both papers that is not really anything

which has any statutory basis. It is more or less custom that puts OPRR in that position. The resources are not provided to OPRR to serve that function. It is something that somehow they cram into an already busy schedule.

Within the rest of the public health system this authority seems to be resistant in other parts of the public health system and outside of the public health system, while it is acknowledged, it does not have any actual enforcement power and is very informal.

There is secondly the point of lack of leverage which I think Dr. McCarthy makes and then Dr. Fletcher underlines and illustrates.

He just mentioned the absence of the budget authority vis-a-vis the internal -- the intramural work and the time that was required to respond to the OPRR's 1990 recommendations. Likewise, the appearance that the OPRR's statement that changes in the assurance were only proposed and were simply ignored. Certainly that indicates a lack of leverage, no fear of contradicting this group, of ignoring them.

The conflicts of mission which were at the center of what I originally was pushing are underlined this time, I think, by Dr. McCarthy as much as Dr. Fletcher and it is interesting -- it was interesting to me in Dr. Fletcher's paper to see a quotation on page 19 from

testimony by Dr. Varmus in response to the GAO report insisting that OPRR had freedom and that it was independent of any oversight of the people concerned with research because the lines of authority of the NIH Deputy Director of Intramural Research and the OPRR Director do not cross within NIH.

I gather that what this means is that in organizational chart OPRR must somehow report to the Director without going through that office and yet as Dr. Fletcher's chart on page 28 shows the actual work of OPRR in terms of having something signed off on goes not only through the Director of Intramural but also the Director of Extramural and all the other management people and the general counsel and so forth and so on. So that is the layers.

I gather that these additional lines drawn on here where they have -- you have the Institute, Center and Division Directors means that it is unlikely that the Deputy Director for Intramural or Extramural respectively is going to sign off before he or she has circulated to those people and gotten their response.

So there is a sense that perhaps Dr. Varmus' statement is truest in one way but it seems to be not representative of the freedom that the office would have in another way.

Now as a matter of prediction Dr. McCarthy says that were the human subjects protection function to be separated from a department it would in his words not survive as an independent agency. We are all dealing with matters of prediction. Were we to follow Dr. McCarthy's view we would not know what would happen the other way. And if we take the other view he may in truth be right.

If I can go beyond now describing what I take to have happened here and just comment on the recommendations to lead off the discussion, it seemed to me that the protection that was being brought by putting the office in the Secretary's office for HHS seemed very thin to me for the following reason just as a sort of an amateur student of bureaucracy.

The insulation that you think would happen, Charlie, comes about because of two things. One that you have a career officer heading it up and not a political appointee. And, two, that it would make a direct report to a congressional committee that would include its account of what is happening and a statement of its own budgetary needs and personnel needs.

Unless the Secretary is absolutely prohibited from having any say what this one particular Assistant Secretary says on these subjects and how it fits into his or her overall budget scheme and personnel scheme and

policy for her or his department, it seems very odd to assume that this report could go forward without having been through the normal processes that everything else does before it gets sent to Congress. In which case it really is subject to all the problems if there is the problem of conflict of mission and everything else that we started with trying to avoid.

If it is insulated then the Secretary has no desire to give it any protection. I mean basically you are on your own. You get to talk to Congress. Talk to Congress. And there is no protection.

What is bought in the process of course is the awkwardness of the relationship to the other departments.

And in Dr. McCarthy's description the body is to include in their annual report an evaluation of the performance of each of the departments and agencies but no authority actually during the year sort of up until then to do anything with those departments and agencies as far as we can see because it is still an HHS office.

And that just -- I mean, it seems to me it puts them in an impossible position of sort of commenting on things and their only apparent power to move people is that they are going to comment on them but they do not have any day-to-day or week-to-week direct authority. If they do, then Dr. Fletcher's recommendation would seem to

make more sense. If they are going to have that direct authority government-wide why should they be lodged in the office of a particular secretary?

I would say that this is the point at which the divergence comes and I think Dr. McCarthy's recommendation means that the upward curve continues upward on a fairly straight line. That is to say if you go back to 1953 with the Intramural Program or 1966 with Surgeon General Stewart's policy statement as to the extramural and place it along in an office and so forth it is fairly even. This would be -- Dr. Fletcher's move changes the shape of the curve and takes it outside of the department.

Since everything that we have seen in both of these reports indicates why it is problematic in its present location the question is isn't this the time then to shift the curve upward and to have that break?

I would only comment that neither of you directly addressed as far as I could see the question of whether there would be in the individual departments some continuing internal office concerned with their own issues and administration. I see nothing inconsistent with the notion of having a national office of human subjects research with the kind of advisory committee that Dr. Fletcher recommends and having each of the departments to

the extent that they support enough research to warrant this having the kind of internal capabilities that Dr. Freeman and our group has been trying to discover if they have now.

I believe that is indeed the same arrangement that happens on the ethics issue, the departments have their own internal ethics officers which implement for the department their ethics -- government-wide ethics policy, but the office of governmental ethics has the overall responsibility to make sure those offices are doing the right things and to address policy issues and questions of interpretation of statutes or regulations.

So there is -- you did not address that but the notion that -- in other words, one might not, in fact, end up obliterating OPRR or some other institute based capability or departmentally based capability for the department. Certainly Dr. McCarthy's indication that you might need to move it up within the department to get the attention of the other PHS components that do not seem to be too ready to listen to NIH might indicate that OPRR itself should go up departmental-wise but that is different from the question of whether the overall function is better lodged in a department.

So that those comments -- and again thank you both very much. It really was -- there are many things I

have not commented on here that I found very illuminating.

DR. CHILDRESS: Thanks, Alex.

Let me see if Charlie or John would like to respond just briefly to anything Alex said and then we will go to Alta.

DR. McCARTHY: Yes, I am sure John wants to make a comment or two and I would too. The first is, Alex, you describe yourself as an unprofessional observer of the government.

MR. CAPRON: Amateur, I said.

DR. McCARTHY: Amateur. I would dispute that but we can have that discussion.

MR. CAPRON: Do you prefer the word "ignorant" to amateur?

(Laughter.)

DR. McCARTHY: No. I would prefer the word "long-time seasoned professional."

With respect to the level of independence I think what you have described does not quite fit the government that I knew from the inside. All budget requests will go up to whether you have an independent office or office within NIH with a line item. They will go up through the Office of Management and Budget which will then get comments and should this ethics office, whatever we call it, be independent then the comments OMB

will get will not only be from HHS, from the Department of Defense, from a number of other cabinet levels, and there will be no one who owns that office to defend it.

So what you are suggesting is that somehow that independence will give them a bigger budget. My suggestion is that HHS, DOD, the Department of Veterans Affairs and other offices will say, "We have no investment in that. It is not our's. We do not -- if they do not do well it is no skin off our nose." So it will be unprotected within the executive branch.

I am suggesting that it would be far better protected if someone owns that office and it is very difficult for a Secretary to disown an Assistant Secretary. So that I think at least you could count on defense from one cabinet level officer for OPRR should it be invested or remain in the department.

So that would be at least a point of disagreement. We are both making predictions about what might happen so obviously I am offering you simply an opinion.

Secondly, I think there is no doubt that the agency heads within the Department of HHS, which fund the vast majority of federally funded research, answer very promptly and without delay to directives from the Office of the Secretary. My experience has been that requests

for action coming from outside agencies are relegated to a much lower level of importance and, therefore, might run into the very kind of delays that John and I both described.

So those are a couple of areas where I would disagree with you. I think the Secretary himself or herself would recognize this now is a very visible office and any secretaries wanting to have a successful career would need to support it rather than undermine it. Particularly if it had strong congressional oversight and support in both houses.

So one has to draw kinds of scenarios about what might happen or would happen but at least the arguments that you and John have raised have not been persuasive to me.

MR. CAPRON: If I may ask just on this last point, I guess our point of difference would then be you would think that the directives or anything coming out of this office if it were lodged in the Secretary's office would get attention within HHS but if it were counted as an outside office vis-a-vis the 16 or so other departments and agencies conducting research it would be ignored. And so the -- I am then put in the position if I agree with you about the ignoring and being worried of adding one more department to that list, and then the question is if

they are going to be ignored are they less likely to be ignored not only in HHS but elsewhere if they come from a presidentially appointed office that is -- has government-wide authority.

You have raised a very good question which is what actions, force and power should that office have and that is not addressed by John Fletcher.

DR. McCARTHY: My answer to that simply is if HHS was a small agency then I think lodging it in -- even at the highest levels within that agency would not give it very much authority or power. But lodging it within the office -- the cabinet office it will get the attention not only in the agencies within HHS but the agencies outside as well in a way that an independent office in my judgment will never command the same level of respect.

I think even -- I think John cites the Government Office of Ethics and it does have a good budget and it has done some good things. I think were it strictly a regulatory office, running into areas where sometimes it must expose shortcomings in the programs at the other agencies and punish that it would have a very different kind of history. It really needs the backing in my judgment of a major cabinet level office. Again it is a matter of opinion.

John and I both, I think, want the same

general result, namely independence with some congressional oversight over an extraordinarily important kind of function that to some degree at the present time is awkward.

DR. CHILDRESS: John, and then I will get Alta and Rachel.

DR. FLETCHER: Obviously Charlie's political philosophy and mine differ. I am not saying that his solution would not work to the end that he desires it to work, that is to protect the regulatory body from attack, from being dismantled. What Congress can create it can uncreate.

But although that danger is always there I think it is still an inherent contradiction and a weakening of the oversight function and the action -- I do have some comments about the action of creating capacity of the agency which I would like to go back to.

But the Nuclear Regulatory Commission and the Office of Government Ethics are not disregarded. They are highly regarded and I think they are effective as agencies. So as a matter of historical record two agencies that were once encumbered by very similar dynamics, the problems have been recognized by Congress, and the -- and corrections have been made.

I think that my recommendation presuppose a

vision of human subjects research that I believe the commissioners share a universalizing of the protection of human subjects of research which our European colleagues have already done and which I feel we are behind in terms of moral considerations and legal considerations of the imperatives of protections of human subjects.

So if the evolutionary -- if the evolution of human subjects research and protection of human subjects is towards universalizing the basis of it and making it equal then the future national office needs to be set up within that paradigm. It needs to be established to have a much larger theater of operation and reconceptualize not within the federal paradigm but within a national paradigm.

This is a major undertaking and will be very unpopular with private funders of research. It will be extremely unpopular but a fight worth engaging in for all the reasons that the first stage of it within the federal sector was worthwhile.

Sixty percent of funding for biomedical research now comes from the private sector. Excuse me, fifty percent. Forty percent from the federal sector and ten percent from the nonprofit sector. I reviewed these figures recently for a meeting about women's health research. So the fulcrum has changed. The fulcrum of

financial power, of economic power is no longer within the federal sector. It is within the private and nonprofit sector. The country needs a new national office.

Professor Capron's further helpful comments about the -- about having a vestigial or a remainder of OPRR within NIH, indeed within each agency, indeed this is a pattern within all universities that have any kind of -- any major investment in human subjects research is there is an officer in charge of that concern and more staff to help their IRB members and the many ethics committees that major universities now have.

So there is an infrastructure already there that does not have to be dissolved. In fact, it would be necessary to continue. But all should be responsive to a higher authority that acts on behalf of the nation in a more protected and independent location.

Both of the agencies, Professor Capron, that I mentioned have abilities that would strengthen OPRR's successor. They can propose and finalize regulations in the Code of Federal Regulations, visit and/or audit their clientele, promulgate guidance and educational materials for consumption by their clientele and independently govern pertinent activity within another federal department or agency.

This would be some of the action producing

capacities of the new office.

DR. CHILDRESS: Alta?

MS. CHARO: First I want to reiterate the gratitude for enormously illuminating and provocative papers and a real jump up in the level of inquiry that is possible around this table.

Second, although I am not a seasoned government employee, I consider myself lightly salted as an observer. So I want to preface my remarks by what may seem somewhat paranoid but it has to do with conflict of interest for NBAC itself.

I do not know if anybody shares this sensation but I feel slightly constrained on this particular topic specifically because of the position of NBAC and its charter within the whole federal scheme of things. We have an acting executive director who works as an employee at the Office of the Assistant Secretary for Planning and Evaluation of HHS at the same time that we are talking about things that fundamentally affect HHS, its organization, its image, et cetera. In the job description for a permanent executive director is the requirement that that executive director report to that same office even after the permanent executive director is appointed.

We are experiencing the gracious assistance of

NIH on a daily basis. Witness where we are sitting today instead of in a hotel. So there is an awful lot of good will that we depend on from NIH as well as, I think, NIH's revenge by foisting their contract travel agent on us.

(Laughter.)

So I feel somewhat -- I recognize other fellow over travelers.

So I feel like we are in a position of having to rely strongly on our DFO sitting to my right to bring our message to the NSTC and to the OSTP and the Office of the President despite the fact that we are deeply enmeshed within the single cabinet department that is most primarily affected by these conversations.

And so although this may not sound like it this is me being constrained in my comments about this issue.

With that backdrop to my concerns, first, a huge reiteration about the concern about the fact that any recommendations we make substantively on human subjects regulations, for example the decision making capacity of people, will be aimed at the OPRR for the moment since it is the only office that can actually write regs for proposal purposes at this level and then will have to get reviewed not only by all these people but specifically by the division directors in charge of doing research

specifically on these kinds of people.

We know the history of the consent auditor proposals in the past so I want to reiterate the concern about that.

DR. McCARTHY: Could I interrupt just a moment? I appreciate what you say is largely true but do not forget that a major segment of the research in the private sector is regulated by FDA that is gathered around in the audience here.

MS. CHARO: All true.

DR. McCARTHY: So that covers a major chunk of those statistics that John gave a little while ago.

MR. CAPRON: The sights of many rifles are aimed at a chair across the table. Not just the NIH.

(Laughter.)

MS. CHARO: But I want to just pick up on three specific points that were raised so far in the conversation. One is that part of this conversation has to do with the ability of an office in charge of protecting human subjects to affect all cabinet departments through various actions, force and mechanisms.

Now we are going to be hearing later on today about the fact that we have, for example, in the Department of Justice an interpretation of key terms that differs from what casual readers might think of as being

the natural definitions of things like research and such.

It is my understanding that the legislation that now exists and the regulations that now exist specifically grant authority to each independent department -- each department independently through their secretaries to interpret those key terms. So that right now it is not just the positioning of the office but it is the very way in which the notion of human subjects protection is constructed to the legislation that specifically decentralizes interpretation of key terms.

I was wondering if we could in the conversation try to deal with that question at the same time that we deal with the position of the office because position of the office is irrelevant if the departments have independent authority over key interpretations.

The second point I wanted to throw out for your comments has to do with the notion of an independent agency and I do not know the difference between agency and an office so I am going to use those terms indiscriminantly but it may not be accurate to do so.

Among the possibilities you have mentioned so far are new office or putting it within a department, probably HHS because that is where the bulk of the big invasive research goes on. But there is an additional possibility, which is to stick it inside an existing

office that already has some power and some influence, right?

And the Office of Government Ethics is one possibility. OMB, which I know is just barely above the IRS in popularity, is another possibility because it, too, wields enormous authority across the government and through legislation that gave it more power than it does now have this kind of capacity to function in this kind of a fashion.

I wondered if you could -- I wonder if you can comment on the possibility of existing offices. I understand that there might be a particular issue if we do move forward with what we did resolve to do which is to universalize protections to privately financed research that is not already voluntarily as pledged to government standards, that putting things within something like an Office of Government Ethics might pose a challenge because now that office's jurisdiction has been -- the jurisdiction is not wide enough to accomplish those private activities.

Finally on the action forcing thing, I wondered if you could speak to, among other action forcing things, the potential importance of what kinds of committees in Congress and what kinds of review gets done. You talked about annual reports which clearly have a

publicity value but my extremely brief experience on the Hill at OTA led me believe that the only place that has real power here is the corporations and that everything has to do with money and if your money is threatened you will do anything you have to do. If your money is not threatened you will just shuffle paper. That is, of course, hyperbolic but that was, you know, not too far from my experience.

So I throw those out just to kind of season the discussion.

DR. CHILDRESS: Is it unfair but I will ask for brief responses since we are going to need to bring this session to a close fairly soon.

DR. McCARTHY: First, with respect to the separate regulatory authority, when we tried to develop a Common Rule we found that there is no -- at the present time and in the present circumstances -- no central office anywhere in the government, even in the White House, that can issue regulations. Each agency has its own regulatory power.

My guess, and it is only a guess, is that were one to propose a central regulatory power that it would be opposed by every agency within the U.S. Government and, therefore, the chances of getting one would be very slight or slim. Again that is an opinion. So, yes, in the best

of all possible worlds I would have a single set of regulations governing all.

In the way our government is established traditionally one would -- it would be a major eruption and I sincerely doubt whether it would be a successful effort or whether your recommendation if you were to make it would be taken very seriously. So as a practical matter I would say not a very good idea. As a theoretical matter I would say it is excellent.

MS. CHARO: Well, I am a professor you know.

DR. McCARTHY: Yes. So that is the first comment I would make.

Secondly, I think I would agree at least in part if money is involved agencies respond. But OPRR rarely affects the money of any agency in any dramatic way. Therefore, what it has to be able to do is to embarrass the agency in other ways. Publicity about ethics, even though these days we perhaps have a surfeit of it in our public areas, it still is front page news and, therefore, I think it should not be discounted as an element. It needs to be used wisely and sparingly and adroitly but it is a powerful element. And because OPRR does not directly affect very much funding what it can do is shut down an investigator, an office or a specific kind of research, and that affects money, but it is not likely

to shut down an agency anywhere. Absent that it is not going to have the kind of power within government that I think OMB, for instance, would have.

And then my final comment, and John may disagree on all these points, my final comment would be that the long tradition of OMB is that it has never been anything but a politically sensitive office. Therefore, in the kind of subculture that different agencies develop, and we learned a lot about that when we did the Common Rule. We found out it would be easier to make peace in the Middle East than to negotiate regulations across agencies or almost that much. Each agency has its own subculture and the subculture of OMB would be hostile to the kind of principled approached that I think we all would like to see within OPRR. That again is an opinion and OMB might bridle at my saying so but that reflects my own experience in interacting with that agency.

DR. CHILDRESS: John, another brief response.

DR. FLETCHER: Just on your idea, Alta, of possibility of locating a new office within the context of the Office of Government Ethics. In my interviews several other people made such a suggestion as a compromise especially in the present climate in Congress where the feeling is broadly among people I interviewed is that politically this would be very difficult to bring about

unless the White House and the department strongly came out in favor of this.

I think that this possibility should not be overlooked because to the extent that NIH is an executive department and to the extent that the Department of Health and Human Services is involved in the problem that Charles and I described and both the White House and the department are involved, they cannot deny that they are largely the parents of the problem, they should be part of the solution. But given the present climate of not wanting to create new government agencies several people mentioned that as a halfway measure relocating a new OPRR, a new national office, alongside the Office of Government Ethics, which does have stature and does have good funding, would be better than a continuation of the same location and possibly better than Charles' solution, which is to keep it within the department.

DR. CHILDRESS: Rachel, and then what I am going to do is bring this discussion to a close after Rachel's question or comment, and responses of John and Charles.

DR. LEVINSON: I guess rather than a question this is really comments and echoes and reminders on what the two speakers have just said. John's point about having -- moving to a national paradigm from a federal

paradigm is very important, that if you are as a commission considering expanding the Common Rule protections or other forms of human subjects protections to the private sector that it would be wise to do that and to develop this model in that context. That can be done while keeping the office within the Department of Health and Human Services.

As you pointed out, FDA regulates the private sector but only if you are focusing on biomedical research. We have to remember that there are 16 other agencies that are signatory to the Common Rule and many of them are not focusing on biomedical research and a number of those agencies continually remind the group that works on implementation of the Common Rule that you try and work beyond just the biomedical model. There are other forms of research that perhaps might not be overseen appropriately within HHS.

The other issue is if you do that within HHS it leaves out the other departments. And the point, I think, has made pretty clearly -- although, Charlie, your feeling is that if it is within a large department that other departments will listen, other secretarial cabinet level departments will listen. But there is no authority. Listening I do not think is enough. An embarrassment, while useful, is not necessarily enough and that is a not

a formal change that can be pointed to.

So I think there are a number of good points that have been raised but you have to think about the limitations of each of the models.

DR. CHILDRESS: Charlie and John, do you want to respond?

MR. CAPRON: Could I ask one question of clarification before we lose you? Charlie, you have the examples of things like the Klein and Gayle situations. My impression was that while OPRR reached a conclusion that any debarment or anything else that applied to those people or cutting off of funds would have come from whichever institute was funding them or from the NIH Director's office but I may be wrong. Is that something that OPRR itself has the authority to do directly?

DR. McCARTHY: Yes. OPRR has actually shut down at least in the animal area, but I think the animal is clear, the entire research program of a whole institution. Now it has to do that by interdicting the research funded by each of the institutes throughout the NIH but none of those institutes could continue funding unless OPRR lifted the bar. So, yes, it has pretty good authority to shut down research even -- and some of those institutes grumbled and complained but they all complied.

MR. CAPRON: Does it have similar authority

vis-a-vis the funding going to individual researchers within NIH?

DR. McCARTHY: Within NIH, no, because these are salaried employees and their research budgets go to an office. Yes, we could shut down a whole unit within but it is very difficult to get at it by the mechanism of funding. It would have to go through administrative channels because the funding does not flow through the same kind of channels as grants or contracts. It goes to the institute and the institute apportions its budget in a very different way than through a specific amount set aside for a specific project. So, yes, I think we could shut that down. In fact, I think we threatened to do that with Dr. Gallo's office. But it would have to go through slightly different channels.

MR. CAPRON: Thank you.

DR. CHILDRESS: Thank you.

DR. McCARTHY: When I speak "we" I sometimes forget I am still not -- I am not at OPRR.

MR. CAPRON: Right, I understand.

DR. CHILDRESS: There are still traces.

Thank you both very much. You are welcome to stay around for the subsequent discussion and we are going to have Joan Porter with the history of interim period between proposal and adoption of the Common Rule but I

know that you both have other obligations as well but we thank you very much for joining us today and for the paper you submitted.

Before we turn to the other subject, though, I wonder if I could ask Alex and Alta to put their heads together at some point and to talk about a way to proceed with the discussion we have just heard and possible recommendations to work out with staff. So what you would like to bring before us as a kind of proposal and I will be glad to join you on that. But if that is okay with the subcommittee I would like to proceed that way.

Thank you again, Charles and John.

Okay. We have a discussion with Joan Porter with the Presidential Advisory Committee on Gulf War Veterans Illnesses and formerly of OPRR to talk about, as I mentioned, the history of the period between the proposal and adoption of the Common Rule, and this is something that grew out some recommendations that Alta Charo brought before us.

Thank you very much for joining us today.

HISTORY OF THE INTERIM PERIOD BETWEEN PROPOSAL AND ADOPTION OF THE COMMON RULE

DR. PORTER: Thank you for asking me.

I am going to discuss the Common Rule, sometimes known as the federal policy or the federal-wide

policy for the protection of human research subjects. Sometimes it is incorrectly referred to as the model policy still.

Dr. Childress asked me to present a perspective on why the Common Rule was created and why it took so long to craft a response to the first recommendation in the first biannual report of the President's Commission on the Study of Ethical Problems in Medicine, Biomedical and Behavioral Research, also what were some of the difficulties for the departments and agencies in their implementation strategies.

(Slide.)

I am presenting from the perspective of the Executive Secretary of the committees that coordinated the creation of the Common Rule. I served in this position from 1982 until 1995 at which time I took a position on the staff of the Presidential Advisory Committee on Gulf War Veterans Illnesses which is going to end this week.

I did bring some copies of excerpts from the preamble from the 1991 Common Rule Federal Register publication for you if you need to refer to them at some time in your deliberations to get specific dates of events and specific names of organizations and committees involved.

In 1981 the President's Commission issued its

first biannual report on the adequacy and uniformity of federal rules and policies and their implementation for the protection of human subjects in biomedical and behavioral research. In part, this was based on staff work accomplished by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

(Slide.)

The first recommendation of the President's Commission first biannual report was as follows: The President should require through appropriate action all federal departments and agencies adopt as a common core the regulations governing research with human subjects issued by the Department of Health Services, HHS, as periodically amended or revised while permitting additions needed by any department or agency that are not inconsistent with these core provisions.

Public Law 95-622 required the departments and agencies whose rules, policies, guidelines or regulations were affected by any commission recommendations to publish in the Federal Register and to receive public comments. All this was to have been done in 180 days and in reality it was more like 180 months before an adequate response to the commission's recommendation was made.

Since 17, I recall it was 17, federal

departments and agencies were identified by the commission as being affected major redundancy would have been involved in the Federal Register publication.

Dr. McCarthy, then Director of the Office for Protection from Research Risks, OPRR, approached through channels the Office of Science and Technology Policy that agreed to have HHS publish the recommendation on behalf of all the federal departments and agencies. HHS was chosen as the department whose policies would serve as the basis for all of the others. It was not the only game in town but it just about was the only game in town.

It was the department that had first issued regulations and had the most experience with history and human subjects protection issues. As it later evolved, the Office of Management and Budget, as well as the Office of Science and Technology Policy, played a major role in the numerous steps along the way to create a federal policy.

It took from 1981 to 1991, ten years, for the recommendation to reach a major implementation milestone of publication of a federal-wide policy, that is the Common Rule in the Federal Register as a final regulation. In reality it was not a federal-wide policy. Some departments and agencies that might have had or may now have research involving human subjects were not involved

in the rulemaking exercise primarily because the commission's report did not identify them or because the department or agency head indicated that no research involving human subjects was supported by the respective department or agency.

Why did it take so long?

(Slide.)

First, there have been several committee structures created that served to adapt the 1981 HHS regulations as the rule for federal-wide acceptance. The first committee was chaired by the Assistant Secretary for Health in the Department of Health and Human Services, Dr. Edward Grant. The Office of Science and Technology Policy set up this committee with representatives of departments and agencies affected as an ad hoc interagency committee under the Federal Coordinating Council for Science, Engineering and Technology.

As I said, the goal was to use the HHS regulations as the basis for creation of a policy by which all the departments or agencies could abide. That meant to have a common policy HHS had to be open to some modifications in its own regulations to accommodate the needs of the other players.

Along the way the ad hoc committee evolved into a fully chartered committee under the Federal

Coordinating Council called the Interagency Human Subjects Coordinating Committee. The head of OPRR became the committee chair rather than the Assistant Secretary for Health.

When the final rule was published in 1991 the committee became the Human Subjects Coordinating Committee of the Committee on Life Sciences and Health of the National Science and Technology Council.

The idea of the biannual report recommendation was to have a common core policy. That core concept really became along the way more like a common policy or a common rule. The benefits were thought to be numerous in devising a common approach in deciding how to implement the commission's recommendation. The idea of an executive order was explored but the ad hoc committee moved to the concept of a model policy that each of the affected departments and agencies could adopt.

The policy idea was appealing because some of the numerous details encompassed in the federal regulations could be tailored to departments and agencies' needs that could not be so easily addressed in an executive order.

A federal policy could potentially do the following: Cover gaps in federally supported work whose departments and agencies had no human subjects protections

in place. Replace ill-founded, obsolete or incomplete policies. Lift an administrative burden from institutions, investigators and institutional review boards, IRB's that would potentially have to deal with 17 different departments and agencies with 17 different policies and rules.

A federal-wide policy could also save the other federal departments and agencies from having to reinvent the wheel. They could piggyback on to the HHS experience in some but as we will learn not in all senses.

So the committee started down the road of a model policy. A drafting subcommittee of the Interagency Committee assembled and met regularly to address every line in the HHS regulations Subpart A. Subparts B, C and D of the regulations were not the focus of any of the discussions for the first stab at the model policy except peripherally perhaps. You recall that subparts B, C and D had to do with special protections for pregnant women and fetuses, prisoners and children involved as subjects of research.

The drafting subcommittee, frequently hosted by the National Science Foundation, consisted as I remember of the Department of Health and Human Services, the Food and Drug Administration, the Department of Defense, the Environmental Protection Agency, the

Department of Energy, and the National Science Foundation representatives.

Bill Dommel played a major role with the regulatory redrafting of the then version of the HHS regulations incorporating suggestions by members of the subcommittee to clarify meaning and to accommodate different organizational operations.

The National Institutes of Health legal advisor, Robert Lanman, also participated in the process.

A quite obvious groundrule advanced by the HHS representatives was that the HHS regulations would be changed as little as possible. The 1981 words in the regulations had a specific meaning with the research and institutional communities. Messing with the words "unnecessarily" could send unintended repercussions to those communities.

I would like to give you an idea of some of the specific department and agency redrafting issues. In the drafting subcommittee there were numerous needs that were never anticipated. One of the first major issues concerned the Food and Drug Administration. The section on assurances, Section 103 in the regulations, and other sections, had to be rewritten around the Food and Drug Administration. In its capacity as a regulatory agency considering investigational new drug exemptions it had

more of a spot check up after the fact approach. No upfront assurances as described in Section 103 on assurances in the HHS regulations.

The Food and Drug Administration's regulatory relationships were with sponsors and clinical investigators rather than institutions as reflected in the HHS regulations. The Food and Drug Administration and HHS had a long history of working together to make compatible if not identical aspects of their respective regulations to address human subjects protections. So I would characterize this aspect of redrafting as time consuming but there was a good understanding of what needed to be done.

Another dilemma was raised by the Department of Defense. Representatives from this department were concerned about the assurance negotiation in Section 103 as well. The military ethos involved everything ordered to be done from the top down. The Department of Defense representatives wanted some language that they might be able to use to interpret that a Department of Defense directive as to what would be done with regard to human subjects protections could be equivalent to an assurance flowing upward from a component of that department. Ultimately this was not the way the Common Rule was implemented but this aspect of the deliberations took

quite a bit of time.

Along the way there were other lengthy discussions about definitions such as minimal risk, about covering foreign research, inclusion of both genders on institutional review boards. Some of the wording that may seem esoteric to users of the regulations has a long history of negotiations. For example, I cannot tell you how many hours went into the crafting of the regulatory provision regarding IRB membership that states that "every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes so long as no selection is made to the IRB on the basis of gender." There is a long history to that one.

The section of the HHS regulations that involved the most dramatic changes was the section on exceptions, 101B. Some exemptions were combined with others and/or reworded. The exemptions are tricky. What I mean by tricky is that they are difficult to understand and confusing to apply in my view. They were tricky before they were modified and they still are tricky but I think they are better after the redrafting.

It took considerable discussion on the part of the subcommittee members to grasp some of the subtleties

and nuances of the exemption section before we could even begin to entertain any modifications there.

In addition, over the course of the request for clearances and approvals from the departments and agencies a new exemption on taste testing was eventually drafted. That is Section 101B6. This had to be carefully coordinated with the Food and Drug Administration, the Environmental Protection Agency, and the Department of Agriculture because each had different terms of art and legislative authorities conveying varying meanings towards like "safe" or words like "approved."

Also created was a part of an exemption regarding confidentiality for supposedly applying only to a specific program of the Department of Justice. That is exemption 101B32. I am not sure that the Department of Justice today knows exactly the applicability of that particular exemption feature.

Further delays: Based on our work in the committee, on June 3rd, 1986, the Office of Science and Technology Policy published for public comment in the Federal Register a proposed model federal policy for protection of human research subjects finally. To effect this publication we were really plowing new ground. The federal-wide policy was a new type of animal in many senses. We need to work closely with the Office of the

Federal Register, with the Office of Management and Budget, and with the Office of Science and Technology Policy to figure out how to have the most efficient clearance procedure for 17 federal departments and agencies with regulatory making delegations and authorities and Code of Federal Regulations sections.

Much of it got made up as we went along. The Office of Management and Budget helped cut some paperwork corners for us but there was still plenty of paper. To publish in the Federal Register we had to have signatures from 17 federal department and agency heads or those to whom they had delegated authority. Believe me just finding out to whom they had delegated authority was a major fete.

The regulation had to clear 17 different regulatory processes. Members of the drafting subcommittee, an ad hoc committee and chartered committees by and large worked hard and stayed with the process. But in almost all cases these were personnel who were in the echelons in the organizations in which research was conducted or supported. Persons who knew something about clinical research but persons who were not in the outer offices of the department and agency heads.

To clear this first model policy proposal there was a massive effort needed by the representatives

and the committee leadership to educate officials up and down the line in each one of the departments and agencies about the background of this proposed policy and about the new logistical clearance details that have been cut with the Office of Management and Budget like the Paperwork Reduction Act.

These were officials who knew nothing about human subjects research and had other pressing priorities. You must remember that we did this clearance process not once but three times. Once with the proposed model policy, once with the proposed Common Rule, and once for the final rule.

In the course of that time frame we had, I believe, three different federal administrations. Therefore, we had 17 sets of new officials to educate and persuade that this was important to do each time there was an administration change. There was also turnover in the Office of Science and Technology Policy so that we lost some of our most powerful influence to get this done and we had to recultivate this influence more than once.

In addition, during the ten-year period the Office for Protection from Research Risk moved from the Office of the Deputy Director, National Institutes of Health, to the Office of the Deputy Director for Extramural Research where the support, attention and focus

on the Common Rule Project was perhaps diluted somewhat in favor of more National Institutes of Health specific fiscal and mechanism issues.

Departures equaled delays. There was a change all around us in some senses but there was some stability in the Office for Protection from Research Risk, the members of the interagency committee, and the Office of Management and Budget representatives who did have a real commitment to seeing this through.

When the proposed model policy was issued departments and agencies expected that they would be allowed to take departures or deviations from the common core policy to meet the peculiarities of their own organizational ethoses, historical events, legislative mandates and research systems.

(Slide.)

Recall again the language in the original President's Commission recommendation. The federal departments and agencies adopt as a common core the HHS regulations or permitting additions needed by any department or agency that are not inconsistent with these core provisions. The departments and agencies wanted a plethora of departures all carefully crafted in legalese. All eroded the spirit of uniformity and in some cases protection commitments.

The Veterans Administration led in the number of departures as I recall and the Department of Education followed. The Food and Drug Administration had departures and even the HHS had departures from what had been its own regulations.

To condense a long story the Office of Management and Budget officials insisted and persuaded the Office of Science and Technology Policy officials to insist on one driving principle, uniformity. Not a core but uniformity. No departures.

(Slide.)

In the face of all of the proposed departures the departments and agencies had cooked up the Office of Management and Budget moved us from a model policy to a Common Rule or regulation. The common regulation had something with teeth. In other words, a mechanism that could not be so easily manipulated with interpretations and deviations by the departments and agencies without the scrutiny of a central authority in the form of the Office of Management and Budget.

So the concept of the model policy was dropped and a regulatory mode became the vehicle of the next years.

In the ensuing time the Office of Management and Budget held a line on individual department and agency

departures. It simply refused to publish or entertain any deviations for the final rule that were not grounded in explicit legislative requirements imposed on the departments or agencies. Some of the proposed departures were done away with through a redrafting fix in the rule so that there could be some wiggle room such as the Department of Justice exemption creation that I mentioned earlier.

Eventually the Department of Veterans Affairs dropped flat out all of its recommendations with some pressure from the Office of Management and Budget.

The Department of Energy representative pushed the other representatives in every way possible. The Department of Energy had a special problem. The Human Subjects Protections Regulations and directives that the Department of Energy did have on the books were based on the original 1978 HHS regulations and they were quite unworkable. The Department of Energy had some pressing and visible human subjects protections problems to address by regulatory revisions in the Common Rule drafts but these revisions were being held hostage by the other departments and agencies' failure to drop departures they thought they needed.

The Office of Management and Budget would not let one department or agency publish unless all did in a

common uniform rule.

In all candor I will tell you that the single most difficult set of negotiations from my perspective was with the Department of Education. The Department of Education did drop some of the departures it thought important over the years but the publication of the final rules literally held up for over a year regarding a few words in the section on Institutional Review Board membership requirements that symbolized a profoundly held set of personal and departmental values. It finally took the President's Science Advisor, himself, with intervention from high levels in OMB, Office of Management and Budget, to create a compromised solution.

The issue had to do with the composition of the IRB.

Now OMB did have an interest in the thrust and tone of the regulations as well as substance. The goal was to make them as little onerous as possible on the institutions. Remember the 1980's was an era that took on a mode of deregulation and minimization of governmental requirements on the private sector. In the section of the regulations that had to do with Institutional Review Board composition the 1981 HHS regulations we were working with as our starting point indicated that "if an IRB regularly reviews research that involves that vulnerable category of

subjects, including but not limited to those described in subparts B, C and D, the IRB shall include one or more individuals who are primarily concerned with the welfare of these subjects."

The Office of Management and Budget influence rechanneled the regulatory requirement to drop the term "welfare" all together and substitute instead that "if an IRB regularly reviews research that involves a vulnerable category of subjects such as children, prisoners, pregnant women or handicapped or mentally disabled persons consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these individuals."

The Department of Education would not go along with this language. It did not sufficiently protect handicapped children in the view of that department. The Department of Education had originally proposed many departures they had dropped along the way. This was their last remaining concern.

The final compromise was the publication of one departure to the rule by the Department of Education. "When an IRB reviews research that purposefully requires inclusion of handicapped children or mentally disabled persons in the research sample the IRB must include at least one person primarily concerned with the welfare of

the research subjects."

It is not my purpose here to comment on the merit of the issue but merely to illustrate the nature of some of the negotiations that delayed us in promulgation of the final rule.

(Slide.)

DR. CHILDRESS: Because of our time constraints we really -- we had talked ten minutes and --

DR. PORTER: Okay.

DR. CHILDRESS: -- and we are about double that now.

DR. PORTER: Okay.

DR. CHILDRESS: We will need some time to interact with you and we may just have to do most of it by reading it.

DR. PORTER: Okay.

DR. CHILDRESS: Unless you can move through pretty quickly.

DR. PORTER: Let me hit the high points here in giving you a couple of observations.

First of all, OPRR or HHS for that matter was not and is not empowered to require compliance with the Common Rule on the part of the departments or agencies. It exerted influence by explaining, cajoling, coordinating. A major mechanism to do that was through

the Human Subjects Coordinating Committee. There is no direct provision for the Secretary, HHS, to exert authority over the interpretation of another federal department's or agency's regulations nor is there a direct way HHS can make the departments or agencies implement the rule.

There is, however, a more indirect but quite important influence of the Office for Protection from Research Risks, that is HHS. The Office of Management and Budget's effort to minimize paperwork for the regulated institutions and the federal departments and agencies resulted in its insistence that the Common Rule require the federal departments and agencies accept the HHS multiple project assurances negotiated with the research institutions with which HHS has a lot of research business rather than having each department and agency negotiate with these institutions their own forms of assurances.

OPRR, therefore, had the potential of holding the line on interpretation of the regulations involving research conducted or supported by all of the departments at those institutions holding HHS multiple project assurances. These assurances required by and large that all research at the institutions be carried out in accordance with HHS regulations and assurances.

(Slide.)

I will move quickly here to summarize a couple of other observations. First of all, everyone is tied to everyone else. If one agency wants to move they all have to move. If the Department of Energy needs a regulatory modification regarding classified research all must be involved. There are some technical ways around this but the principle and the problems should be evident.

(Slide.)

I would like to give just a few observations and hypotheses on why I believe implementation of the Common Rule has been nonexistent or minimal in some of the departments or agencies. Has what has been done enough? I think that depends on our perspectives, our values and our priorities. If the departments and agencies did more by way of education, assurance negotiation, monitoring of institutions would human subjects be better protected? Would potential for a violation of rights and welfare of human subjects lessen? I am inclined to think so but I am not sure quite how to assess this.

With the understanding that I have not been working with the Human Subjects Coordinating Committee for the last two years I would like to give you a list of implementation complications that the departments and agencies faced and probably still do face.

(Slide.)

These are lack of access to echelons to effect implementation through commitment and resources. I think there is a view that the Common Rule was intended for research such as the National Institutes of Health or the Department of Health and Human Services has but activities like surveillance, demonstration, social sciences, evaluation, focus groups, this was not seen as under the purview of the Common Rule by many persons. The definition of research in the Common Rule is quite broad.

I think that the department and agency personnel understood its applicability to HHS types of research. They might understand Tuskegee but they really failed to see the relevance of protection of research subjects in their own activities.

A second problem was that representatives on the coordinating committee were for the most part not full-time working on this issue or responsibility and pay offs for them came through other positions or other responsibilities that they had. There were some quite dramatic exceptions but generally that is what was the case.

I think a major complication in the implementation was that there was confusion early on about how much OPRR could do for the other departments and agencies. Some of the departments and agencies thought

that because the Common Rule required acceptance of the HHS multiple project assurances that OPRR was going to do all the work of negotiating all of the assurances for all of the departments and agencies and that OPRR would not do this came as a big shock to some of the departments and agencies.

I think OPRR's staff tried to be as responsive as we could but in the face of our own workload there was not too much more that we could do than facilitate the coordinating committee meetings, provide advice and encouragement on the telephone from time to time, cosponsor an occasional educational workshop and attend an occasional meeting to support another department or agency representative. It was really having a tough time trying to sell the implementation message.

(Slide.)

Other problems which for time sake I will not elaborate had to do with lack of clarity in the regulations especially I think in the exemption section. That is really hard for departments and agencies.

One to be unnamed agency decided in its implementation proposals that blood drawing is survey research and that that could be exempt under the regulations, for example. That really was not in my view compatible with the intention of the exemption.

I think another implementing problem had to do with evolving technologies and perspectives. There are a lot of new things on the horizon such as repository research, data sharing capabilities, new types of devices and techniques that might qualify for expedited research. These make it exciting for all who have to implement these regulations but it is difficult if you are the only person in your department or agency who is able to deal with this. The staff in the OPRR have relatively easy access to each other, to the ethics community, to the scientific communities, and to well-informed legal advisors with whom to check out interpretations, history, precedence on applications. But the representatives of the other departments and agencies by and large do not have those kinds of advantages so readily.

Last, department and agencies may have special issues. The National Aeronautics and Space Administration, Department of Defense, for example, who have programs whereby employees who by their very employment responsibilities are participants in research activities almost on a daily basis. For example, human factors research. So it is challenging to think how to apply the regulations to those type of situations.

I have numerous other examples of special issues which I will forego.

(Slide.)

In conclusion -- and bear with me, I am trying to condense 15 years of my life here for you. It took many years to develop the Presidential Advisory Commission recommendation into a rule and I hope that this information gives you some understanding as to why it took so long and some suggestions for how similar initiatives might be facilitated. In my term in my opinion it has taken a long time for the departments and agencies to implement minimally the rule even by the most basic of standards.

Could the departments and agencies do a better job in implementing the Common Rule? Yes, in many ways, of course, depending on the reality of a world of limited resources, a myriad of competing value systems, and the resulting scheme of priorities, and criteria that may be fairly soft.

What would it take? Some obvious actions. Commitment from the top of each department or agency, more staff time and resources dedicated solely to these issues, more interagency dialogue and access to others who have confronted implementation efforts.

Is strict implementation of the Common Rule the best way to protect human subjects of research conducted or supported by the Federal Government? That

has been our premise but I think we have to really visit that as a fundamental question.

DR. CHILDRESS: Thank you very much. You have given us so much information and honestly I have to bear responsibility for trying to work in such an important and extended discussion into a schedule that was already set up and thus put a lot of pressure on you time-wise and I apologize for that.

Do you have a copy of the -- is there a way we can get a copy of that? It would be easier if we could get it and share it rather than working from the transcript.

DR. PORTER: Yes.

DR. CHILDRESS: Would that be possible? I think that would be --

DR. PORTER: If I can polish it up a little bit and add some things.

DR. CHILDRESS: Well, we do not even mind receiving it in the form in which you presented it. That would be fine if you would not mind sharing it that way. But I had set aside 30 minutes for this and we still have within that a few minutes so let's see if there are a few questions and comments before we take a break. This was most helpful and something we will want to ponder and think.

First, Alta, did you have anything you wanted to say before Eric?

MS. CHARO: No.

DR. CHILDRESS: Okay. Eric?

DR. CASSELL: Well, in hearing you, I am not sure that when you say could we do better, I was not convinced that better could be done without markedly increased pressure from above. I wonder how that bears on the discussion we have heard earlier about where the OPRR should be placed.

DR. PORTER: I think it does indeed. I think it is quite -- the experience we have had with implementation and are having with implementation of the Common Rule is directly related to the position on the authority for the Office for Protection from Research Risks. There are other factors. Resources of course is a major concern. But it is a coordinating committee.

It is not a -- I would say that the Office of Management and Budget really had the most final and authoritative voice when the Common Rule was implemented in exactly what the language would look like. They had the power to hold everyone's feet to the fire and require the kinds of language that the administrations wanted. Some of these words have to do with policy deliberations and debates about welfare and labor, and things that were

going on in the background that would be difficult to understand.

Alta?

MS. CHARO: Joan, one of the reasons I thought that your presence would be so valuable is because of the data collection and analysis of the federal surveys previously done and of the things that are coming out -- that have come out of that, one finds that the agencies that were engaged in survey research seem to have more frequently than others either interpreted what they were doing not as research or perceived what they were doing as exempt from research that they agreed to regulate or simply have slipped through the net.

I was curious about the degree to which the exemptions that were being argued for at the time that the core Common Rule was being debated reflected this focus on noninvasive, nonbiomedical research, which is survey in nature and for which it is harms associated with breeches of privacy that we worry because I am trying to understand the degree to which the current situation is really simply a reflection of long-standing resistance and perhaps reflects more than anything else a failure to completely address those concerns effectively. That is not meant as a criticism, but address them effectively at the time the Common Rule was adopted.

DR. PORTER: I think there are others in this room who could probably answer that question more precisely and eloquently but I would say that really those kinds of changes came earlier in the regulatory redrafting that took place from 1978 to 1981. The exemptions, although they are a little different today, were basically in place in the 1981 regulations that we used as the template. So some of those issues with the nonbiomedical research community had been hashed out beforehand.

There is a long history probably of trying to encompass the behavioral and social sciences community in the regulations protections as well and I think perhaps that those exemptions reflected some easing of burden or some compromises for the behavioral research community. So those kinds of influences came earlier on in my perspective but they were evident again when we were discussing the Common Rule exemptions.

DR. CHILDRESS: Is there a last question or comment for Dr. Porter before we take a quick break?

Well, thank you very much.

DR. SHAPIRO: Excuse me. As I listened to this presentation and the previous one, both of which were very helpful, the thing that sticks in my mind is C

power. Both of them have described the extraordinary difficulty given the way the government is structured to

really implement even a very good idea and a very simple set of very good ideas just get bogged down in some elements and it is just incredible that this is what you had to deal with.

It is the same thing here said in different words. They tried to describe an effective way to position OPRR.

MR. CAPRON: Wouldn't it be helpful in that regard to hear from people from the Nuclear Regulatory Commission, or the Environmental Protection Agency, or the Office of Government Ethics as to whether positioned differently than OPRR or the interagency committee, whether they have any quicker avenue to have decisions and rules implemented?

DR. FLYNN: It is not just position though. It is also resources.

DR. SHAPIRO: Well, it is exactly that because the -- I remember in dealing with the review of some years ago now, reviewing NIH and its structure in the institutes, it all came back to appropriations and which subcommittee it came to and here you have a whole bunch of them working through here, and that is just the fundamental structure of government here. You are not going to change that. You, therefore, are inevitably left with some of these problems but I think it might be

interesting to hear from some of the people.

MR. CAPRON: I mean, I know with the President's Commission we went to OMB and then we went directly to the appropriations committee. I do not know who OMB may have talked to but our request was never altered by any of that conversation and then we -- I went to Representative Natcher and sat there, was directly examined and --

(Simultaneous discussion.)

MR. CAPRON: What was that?

DR. SHAPIRO: -- usually handles people --

(Laughter.)

DR. CHILDRESS: Well, thank you very much again for -- and we will look forward to getting a copy of the paper as well. Thank you for sharing with us.

All right. A quick five minute break and then we will pick up our last task of the day.

(Whereupon, a brief break was taken.)

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E V E N I N G S E S S I O N

DR. CHILDRESS: The subcommittee is ready to resume. I thank everyone for his or her endurance, patience, understanding, et cetera. We are now going to deal with the Report on Survey of Federal Agencies and I have to thank again, as I have so many times before, Bill Freeman, Susan Katz, Joel Mangel, Emily Feinstein, Everson Hull, and Sean Simon, and everyone else who has been involved.

You recall last time that we had to deal with -- we raised several questions by the subcommittee about matters needing further explication, some descriptive materials that could help you get a sense of how much research was involved in particular agencies or departments and so forth getting a clearer picture of the ball park.

What we are going to do this afternoon is Bill is going to -- and any other members, Bill I see at the table and Emily, any others who have been involved, help us get a better understanding and by reflecting on the findings and the tentative recommendations that have emerged.

And then as I mentioned our next step will be to get Kathi Hanna involved with guidance from subcommittee members in recasting and redrafting the

material for purposes of the next stage of our -- of developing this report.

So, Bill, you have passed out some materials to us and you want to tell us how to proceed.

REPORT ON SURVEY OF FEDERAL AGENCIES

DR. FREEMAN: I just briefly want to apologize for the lack of editing of the materials. We have had some discussions with the members of the commission and staff that resulted in a change. We had planned on having materials at the end of last week to mail to you. That was when the discussions occurred. So what we did was to in the past week revise things. We had also, however, had planned to meet with agencies and did continue to do so because we thought that was going to be a week to do that kind of work. So we have not been able to devote as much time to polish up what was in the handout that you received last night as we would like.

Summary of the message -- you see the handout and the outline. Summary of the message is to remind you Phase I was structure with higher level people in the organizations. Phase II was process with people at the middle level like IRB chairs.

You have in your handout what we -- this was one of the changes. We developed agency specific summaries. The ones you have are the ones that have been

approved by the agencies. The tables have been approved by the agencies as well as, by the way, those summaries.

In that paragraph for each agency, which I believe the first one is Census, which is within the Department of Commerce, is three basic items of information. What is the scale of the research that is conducted or funded? Defined typically as dollar amount. Also it is projects if we can get it.

Then the middle of it is what is the degree, or really it is a yes or no situation, of implementation of the Common Rule, yes or no. Often with -- as we will -- as we will talk about, there is some complexity there.

And then the last item is changes by that agency in protection of human subjects since the initial interview.

Now if you have had a chance to read the material that you got you will notice that there is a section about tension of two different things that we had to face in terms of our report. One is that we were doing -- the initial idea was to do a snapshot or in scientific terms a cross-sectional study of each agency. At one time what was their status? And that was at the time of the interview.

In fact, our process of developing the report has changed the subjects of our research and they are now

-- some of them were changed. Some were changing along -- agencies, of course, change over time all the time. So they are a moving target and the question of a snapshot of a moving entity, how accurate is it. But in particular the -- starting in September when agencies received our preliminary tables of information, some agencies have been very dramatically paying attention to more than they had been and altering what they are doing in this area.

So the question is how do we combine these two things, the longitudinal study that includes changes versus a snapshot or cross-sectional study. We thought for scientific reasons, among others, of doing the research that we needed to adhere to the original plan, which is a snapshot. But, in addition, include information about changes since that snapshot as well as, by the way, a history before. In other words, if this was a relatively recent change we wanted to know about that. At the time of the interview if things had only been implemented recently we needed to know that information and include that in our report.

That gives us an additional scientific benefit, which is that we can talk about the effect of doing the report and that experience says something about the way the federal government operates, namely as others have mentioned, the threat of disclosure. It turns out to

be it appears fairly strong.

Okay. What were the findings? This is something for -- that the commission needs to weigh? We just presented one way to do it or a way that we think is reasonable but there are many reasonable ways to do it.

The first major finding is that most of the federal government, defining most as the amount of research done in dollar terms, is done under the Common Rule in terms of the structures and the processes. We have not looked at quality of those. That was not our task.

Secondly, that even within that, a more -- as important, an additional point is that there is some exemplary work being done by these agencies. It includes all of what I call the big four agencies, NIH, DOD, DOE, and CDC, not necessarily in that order, that do the riskiest -- you are shaking your head. Oh, I am sorry. NIH, Defense --

MS. CHARO: Well, I am just -- you do not want me to interrupt.

DR. FREEMAN: You can interrupt.

MS. CHARO: All right. I am just -- I am surprised but maybe because I am not understanding the way you are using the word "fully implemented." I mean, I am picking up Diane's specialty, which is actually paying

close attention to language here, which she does better than anybody. But, you know, CDC did not appear to have gotten all of its ducks in a row before it started authorizing that research in Africa that turned out to be so controversial. DOD engaged in a highly controversial negotiation with FDA over the use of investigational new drugs on soldiers in the Persian Gulf.

And so characterizing these agencies as exemplary in light of recent controversies seems surprising to me. That is not to say that they have not got a lot of structures in place and that they do not make a very credible effort, et cetera, et cetera, but that is why I am saying that the word "fully implemented," which could be interpreted as meaning "fully effective," is potentially confusing.

DR. FREEMAN: We certainly need to be very careful about the wording. If you recall I talked about that issue at the time of the interview what was the recent history leading up to it and CDC -- of the four, CDC is one agency that we say had implemented fully the structures and processes but recently some essential elements were done recently before the date of the interview and, therefore, they are in what we call Category 2, that the recency of the implementation calls into obvious question how permanent is it. The other

three seem to have had these structures in place for some time.

MS. CHARO: Right.

DR. FREEMAN: That leaves out DOD and we will have to talk about that when we can talk about that.

MS. CHARO: Right. Where informed consent is not even required for medical treatment let alone medical research.

DR. CHILDRESS: Let me clarify something here, though, you could have everything in place and still have a wrong decision --

DR. FREEMAN: Right.

MS. CHARO: This is absolutely true.

DR. CHILDRESS: Okay.

MS. CHARO: Which is why I focus a little bit on the language.

DR. CHILDRESS: Right.

MS. CHARO: But, I mean, DOD does not require informed consent for medical treatment. When we were looking at this for the Presidential Committee on Persian Gulf War Veterans Illnesses I was amazed to find out that you did not have to get informed consent to treat soldiers under at least some of the services and with that as a backdrop to them doing investigational drug treatment or treatment with investigational drugs or medical research

it makes it problematic in the extreme to characterize it as exemplary in any respect even if they have made good effort.

DR. FREEMAN: Well, what I am talking about again is the structure and the processes implemented being exemplary and that is not to say that concurrently you cannot have structures and processes that are adequate and also that you cannot have bad decisions on any of those.

MS. CHARO: All right.

DR. FREEMAN: One of the two that you have mentioned -- my point is one of the two that you mentioned we specifically have included as a special category. Fully implement on the date this goes back to this agency's change. It has been recently, and recently within the past year-and-a-half, rapid change by CDC. So to say that I give in cross-sectional date that everything is fine would be to negate that history and we have at least included that.

It sounds like we will have to deal with how these statements interrelate with the history that DOD has and we will figure that one out. We did not do that in the report of the draft as you know.

The third -- the second major finding, and again one of the question is what is the balance of these that you will want to put in your report, but the second

major finding is that some agencies, including two that do a significant amount of work, we have estimated it is approximately $800 million of research, some of that with vulnerable subjects, some of it with greater than minimal risk, some of it with greater than minimal risk with vulnerable subjects, had not implemented the two basic parts of the Common Rule that we have since the last time focused on.

Do you have a system of reviewing all intramural research to include an IRB for any nonexempt intramural research? And, two, do you have a system to assure yourself that all extramural, that is to say grants and contracts funded by yourselves or done by others, research has been reviewed by an appropriate IRB and approved by that appropriate IRB? If the answer is no to those that is nonimplementation leaving aside everything else that is done.

Now, we also have included in the report with a lot of footnotes additional things but that is sort of the bottom line of how we define implementation or not. To have those or not to have them. So it is not really a degree. We do in the text talk about additional items of protection.

DR. SCOTT-JONES: Can I interrupt?

DR. FREEMAN: Yes, please.

DR. SCOTT-JONES: I am going to have to leave in just a minute so I wanted to ask a question very quickly. Having just read this after we arrived and were given this, I have not had really a chance to digest this carefully, but it just seems to me that there might be a problem in moving from conclusion I-A to I-B in that in I-A -- under Arabic Numeral I you have a statement about the persons you interviewed. It seems to me that a person might want to be cautious in doing that because by inference it might suggest that the persons you interviewed in the agencies that are not in your judgment fully implementing are not exemplary in their dedication and understanding.

Do you see what I mean? You have a statement about the persons interviewed and a judgment of persons.

DR. CHILDRESS: Page 30.

DR. SCOTT-JONES: Page 30 under I-A-I.

DR. CHILDRESS: Right in the middle of the page?

DR. SCOTT-JONES: You have a statement that some people are exemplary. It is a judgment of persons rather than the agencies and you are going to go on with the next section to make a statement that some agencies may not be implementing and you do not comment one way or another about the persons. By inference you might be

saying that the persons are not exemplary and we were not to judge persons, were we?

DR. FREEMAN: One of the things -- that is a good point and when -- if you would see where you are at that point when you do have a chance to read it, one of the things we found was in addition to structures and processes it appeared, and it is actually along some of the things that the review of Eric's book talks about, is that it seems like the behavior of some people, at least as was described to us, seemed very important on a one on one basis to help researchers learn how to do it right and what was the importance of ethical research -- of ethics in research.

The mentoring system.

There was also examples of people higher up who made it a priority to get a good system in place and maintained. Yes, it is in distinction not to individuals. We purposefully did not say individuals because we did not know who they were nor did we want to and we did not think it was appropriate to say individuals. But to agencies in which the first subset of that group that does not -- the agencies that did not implement, lack of priority.

For whatever reason the agency -- some agencies have exhibited a lack of priority to implement the regulations. And it seems to me appropriate to lay

that at -- and Bill Raub would say this, I believe, if he were here -- at the highest levels of executive leadership. He said it to Harold and I.

All we are doing is contrasting people who show that kind of dedication at their level of training researchers in special ways with a lack of priority further up. That may be a problem. You may not want to do that. But if that was --

DR. CHILDRESS: There is a way to do it, though, without appearing --

DR. FREEMAN: I understand. That needs maybe some work.

DR. SCOTT-JONES: Instead of saying "persons we interviewed" maybe some statements about leadership, a little bit more abstract.

DR. FREEMAN: Okay.

DR. CHILDRESS: I think that would be a preferable way.

DR. FREEMAN: Okay. We may need your help on that kind of wording.

DR. CHILDRESS: Diane, any other things you wanted to raise since you have to go?

DR. SCOTT-JONES: No.

(Technical difficulties with sound.)

DR. FREEMAN: That was about -- the first

clause was lack of priority within some, not all, agencies. We define actually lack of priority as agencies that knew they were under the Common Rule -- there is no question about that. No one denied it. They said, "Yes, we are under the Common Rule." And at least six years and in one case 16 years later still have not the structure or the processes in place. It is difficult to say that that is not.

A second problem we found was lack of understanding. There was confusion, I think was our terms, and also disagreements at the same time about what are and should be things like what is research, what is exempt, those exempt categories. How do exempt, like the confidentiality statute, relate to the Common Rule, et cetera?

And then the third thing was we got from especially agencies and departments even that do relatively small amounts of research that the overhead as they understand it to simply implement the structured processes is incredibly high compared to the amount of research they do. And in some small agencies, like the Office of Civil Rights -- I mean, you know, there is only a few people there -- it would be overwhelming. So that they at least do not know how to do that.

Now that is not to say that it cannot be done.

It is just that they are not aware of that.

The were, as you can see in the report, some additional lower level of findings. But those were the two primary ones based on -- and defined in the terms actually fairly closely as I indicated.

The rationales for the importance of nonimplementation was discussed and raised. I include it here. Now, that is different than the scale. The scale is does this nonimplementation occur only in a few peripheral agencies that do hardly any research? The answer is no.

Then is nonimplementation a problem? What are we talking about? What is the importance there? And I have included in the draft some reasons about it. And, in particular, going back to the original National Commission that was set up in order to protect, among other reasons, the research enterprise that the research enterprise was under attack very validly for a series of highly unethical research, perhaps with the Tuskegee disclosure.

And it was very clear by the commissioners that talked about it that this was going to, in effect, be a social contact, they used the term, or a contract between researchers and society. And not implementing those can be seen by society as not fulfilling the researchers or at least in this case the federal agencies

not fulfilling their side of the bargain.

I will tell you personally when this report comes out if it comes out anything like what is here it is going to make my life difficult in the Indian Health Service because Indians distrust research and here is a report saying that the feds have not done what they are supposed to do to protect groups and people. It is going to be brought up to researchers in Indian country. Is that part of what is going on?

And that is one major reason to be concerned about nonimplementation.

Another is that the implementation of regs are to prevent things and especially in a setting where there is mistrust. For historical reasons Indians are not the only ones. One more problem just adds one more nail to that distrust and reinforces it.

The additional findings are -- as well we did not put in that you may or may not want to include come more from Phase II but also from Phase I. There are some opinions about the practical issues of the issue of elevating or not OPRR. Not about what you heard here, not about these -- the discussion here was -- but some practical issues about oversight. How is oversight done in the Federal Government?

And then what also has been mentioned

repeatedly, the limits of the Common Rule, limits of the IRB people, and I think Trey talked about one of them -- we interviewed him -- or a set of them. There are some perceptions that reinforce what the commission is looking at may help give additional about what the Common Rule currently with all the changes that have gone on since 1981 -- these are -- not '91, these are '81 regulations for all intents and purposes. That is 17 years or 16 years old. What do we not deal with and the IRB's on their own they feel trying to deal with them without guidance from some authoritative body like NBAC? So we can add those if you like.

We can also add other things but those I think are the major issues.

DR. CHILDRESS: Thanks very much, Bill.

Joel, do you want to add anything? Okay.

Let me ask -- I know that last time Harold and Eric and I think Alta also raised some questions about the materials we had received. I know that part of what you provided here in terms of the data summaries but also in terms of the findings and recommendations relate in part to those concerns.

Let me see -- Harold, have some of your concerns from last time been addressed?

DR. SHAPIRO: Yes, certainly so. I very much

appreciate the response to this. Some have been addressed. I am still -- I want to wait to hear this discussion but I am still trying to work out in my mind whether we really have the right analytical approach to reform or to change. I understand the data, it was very helpful and it is essential that we understand where we are.

I am not quite sure whether I have heard yet or am comfortable with the analytic approach that might really help project this into some better -- you came right at the end, Bill, and you said, you know, these are 1981 regulations and lots has happened since then aside from whether you can implement it or not and in what way to implement it.

It may be that we have to pay maybe some close attention to that as we evaluate. I understand the first mandate was are they doing this or aren't they doing it. We have some answers to that. But maybe the effective way to deal with that or the responsible way to deal with that is to take that information and direct it into a set of observations that may also deal with some of the modifications that are necessary to protect human subjects, which I think what you are saying is the protection of human subjects is one thing and the Common Rule is another thing all together. They are related of

course. One is designed for the other but they are not the same, are not coincident.

I still feel we are struggling for a way to capture that. That is my sense of it but I want to wait to hear some of the discussion.

DR. CHILDRESS: All right. Alta?

MS. CHARO: Yes, I would like to second that and perhaps continue flushing out how that might work because I know you mentioned earlier today, Jim, that we now have a staff person assigned to kind of take over the drafting of a full scale report that will incorporate all these elements. I mean, all of these elements, the contract reports from Fletcher and McCarthy, and the ones coming in, and Joan's talk as well as this are just means to an end. They are none of them ends in themselves.

It seems to me that there is the fundamental goal of human subjects protection first and foremost when the government is somehow involved. Rachel just reminded me actually about the question of whether or not the Common Rule actually does, in fact, serve to protect people or does it, in fact, hinder human subjects protection.

And we have got, I think, to acknowledge that there is a fundamental possibility in answering that question because we do not have the ability to get

specific answers to the question of how many subjects, how many protocols, how many adverse events that are associated and also caused by the protocols that are covered by the Common Rule versus a control set of those that are not in order to our study in that way.

But we can take the information about the origins of the Common Rule, the obstacles to its development, observations about its current status of implementation from the purview of the paper implementation, the anecdotal evidence about the problems associated with that and whether or not it is actually effective in doing what is designed to do. Speculation about reasons why it is not effective sometimes, some of which will come from the Fletcher and McCarthy papers, in fact a lot of it.

And then I would like to suggest that there is still a missing part of the puzzle in that evaluation and that would be to then get now people from the various agencies that have been trying to implement this to come in and talk with us about both their reactions to what was found in the survey now that they have had a chance to receive this although they did not get a chance to receive it in a fashion that would let them really look at it and talk with us both about their reactions to this as well as to tell us about their perception of the obstacles they

have been facing and what would improve their situation.

So an opportunity, not just a demand that you respond to allegations, quite the contrary, but opportunity to talk about their own frustrations and to feed that into the evaluation of the system. And at the end come up with some set of findings about the degree in which the Common Rule is being implemented and the existing obstacles to its full implementation and our speculations about the limitations that would be faced even if it was fully implemented and actually achieving the goal of human subjects protection.

DR. CHILDRESS: Good. Then you are proposing that as soon as we --

MS. CHARO: I am proposing that Kathi write all that, yes.

DR. CHILDRESS: Except we have to get the agencies and departments in.

MS. CHARO: I think -- I would like to throw that on the table as a possibility because although some agencies have had people come to talk with us and sometimes they have come through the public testimony, five minute resource, I would like to give a more formal opportunity to the agencies to present both their frustrations in trying to accomplish this goal as well as their reactions to anything that was found that suggested

that they are not doing a good job of it.

DR. SHAPIRO: I have heard two different kinds of things here exactly in relation to the issue you raised, Alta. One is that somehow the Common Rule can also serve as an impediment to doing the right thing, whatever that is. I have not heard any examples of that but there could be and I would be anxious to know more about it or the way it is implemented or something in the structure that makes things worse for human subjects than it would otherwise be.

Another is really a case of omission, namely we have not -- we, meaning whoever is sort of focusing on this, OPRR or others -- are not getting out guidance to the IRB's, that they want more. The reason they are frustrated is we, whoever the we is in this situation, simply do not -- have not updated our thinking and have not done things which would have made it easier.

Now are you thinking of those two categories or other categories all together?

MS. CHARO: Well, I think, the possibility that it is an impediment, I think, needs to be acknowledged. I agree with you, we have not heard any specific examples and we have to be open to them if they exist.

DR. SHAPIRO: Sure.

MS. CHARO: I think also the fact that a regulatory requirement exists means it exists in the agencies and they are not free to simply say the issue is not to follow but we are in a position of evaluating sensible -- how sensible the regulation is for the purpose of providing advice.

DR. SHAPIRO: Yes.

MS. CHARO: I guess, I am trying -- you know, Rachel, like I said, did remind me that we are trying to keep in mind two things simultaneously, which is the degree to which there is some implementation of the regulatory requirement, which is at the first level simply having structures on paper and at the second level having those structures actually function, and at the third level -- this is where it dovetails into the next big question -- having them function in a way that actually achieves the underlying goal, which is the protection of human subjects.

And that last question, I think, is the one that leads very naturally into the larger set of issues about how one designs a system that will provide adequate authority within the Federal Government. And you reminded me, and I am glad you did in this whole kind of outline thing, about the importance of incorporating anything that comes out from Charles McKay's survey in time for our

report to use it because of the degree to which the dependence upon a decentralized IRB system is part and parcel of the evaluation of the ability of this set of regs to actually accomplish its underlying goal. That has to be part of the whole picture, too.

DR. CHILDRESS: Bill, and then Laurie.

DR. FREEMAN: Along the lines, I think, to make your contrast very clear, you should read -- please read the report. Please read the report. Have we made it clear? We tried to. The difference or the distinction between the Common Rule and protections, we have tried to say why we think, in fact, the Common Rule is a protection. And those agencies that think they have protection without it, what they have left out by not looking at the Common Rule? If that is not enough or you disagree with whatever, let us know. We have tried to do that.

DR. CHILDRESS: That is another question.

MS. CHARO: Yes, but I think actually -- no, I think what has been developed is going to be extremely useful and I am extremely grateful for it. Not only does it talk about the Common Rule versus actual protection but, you know, in the observation about things like the interpretation of whether or not research is going on there is an opportunity to highlight exactly what happens

when you have from a legal point of view the authority to interpret scattered among, you know, all 17 agencies and, therefore, not only are you likely to get these interpretations but they are what you expect to get. They are justifiable. They are legal. They are supposed to be there. And you get a chance then to say are we happy with that kind of result.

DR. FREEMAN: Right. The other question is that we have not -- we have not tried to address, I do not think as well -- and by the way this is because we tried -- like I said if we have not done it well let us know or, you know -- obviously you will be doing that.

The question of function versus -- the Common Rule versus implementation of the Common Rule. I think it is fair to say that we have from having this discussion paid attention about implementation. We have added from the last time an organization section about the -- what is called the cooperative regulations. And just today I was working on some stuff that Rod had prepared and we will have by the middle of next week some more about how to implement things effectively of this kind of regulation in the federal government.

There is a little bit about improving the function of the Common Rule. There are actually ways to improve it from the implementation end that would decrease

the cost and increase the benefits to each agency. But you may want to really look at that and does that need to be strengthened in a much stronger way about looking at the functioning of the Common Rule and can we say something more about that.

DR. CHILDRESS: Laurie?

MS. FLYNN: Let me just see if what I am hearing tracks with where you are going. First of all, I think we are hearing that implementing the Common Rule in and of itself is not synonymous with always having complete protection in every instance in decision making that would protect human subjects.

On the other hand, it is rather shocking and disturbing how poorly implemented many places in the government after this many years we find the Common Rule to be. And I think one of the things that at least is clear to me and that we may want to make explicit is implementing the Common Rule really wanted to affect a basic culture change in science and you indicated the history upon which this regulatory process was built.

So we talked about creating a real culture shift in this social contract with science and then we proceeded to under resource it everywhere, to give it not the level of priority, not the level of leadership, not the level of respect within a bureaucracy, or the ongoing

protection for its role, and the independence and integrity one would like to see for that role, but the social contract and, indeed, the problems which it was addressing would have demanded.

Consequently, you know, I think it is terrific that we are going to have this kind of disclosure uncomfortable though I am sure it will be in many quarters because advocacy groups, patient groups, the general public interest, and certainly those who are allied as partners with research in the general health disciplines do not really realize that within the government itself we have done such a poor job and we are hardly in a strong place to tell, although I believe we should, pharmaceutical industries and others in the private sector that they should be, you know, doing what we have not seen done well.

We need to recognize that it is a cultural shift that we have tried to get a few people to do from inside and this report, I think, will have the effect of bringing a lot more strength to that discussion and perhaps both inform people who simply do not know, engage perhaps leadership at a new level of urgency about this.

And I guess the other thing I would say is it is useful to hear from people about the problems they have encountered and I think we should.

I am also interested to learn if we can where it has been done well, what did that take. What was required to appropriately sensitize investigators? We have heard today from some of these investigators and they tell me freely everywhere I ask the question, "When we graduated from medical school we had advanced residency training in psychiatry or name that discipline but we never had a course in ethics."

And I mean there are some basic and fundamental gaps between what we are expecting as a cultural shift in the field that plays out in individual decisions around patients and protection and the basic education that goes on at all levels. And so I do think at some point for us to be able to bring forward out of the work that you have done and out of other kinds of dialogue we may get some specific indications of what it looks like when it is done well and what it requires to do it well. And what kinds of specific programs of education, instruction, support, monitoring and reporting enable one to feel that somebody -- while not maybe yet exemplary -- is at least -- has the apparatus and the personnel adequately trained to do the job that this very important social contract asks for.

MS. CHARO: Good idea.

DR. CHILDRESS: Arturo?

DR. BRITO: There is one big piece of the puzzle that I have not heard here but I am going to go back and summarize what I am hearing. Basically the first big portion of this is that we have to determine the value of the Common Rule in itself. And, Alta, you raised the question of whether or not it is truly protective or not. But I have not heard that it is not protective but we have to obviously determine that first and go from there.

And then I will touch on what Laurie was saying about the method of how to best implement it and how has it been implemented and what has been the -- what methods can be best utilized to increase implementation assuming that it does have value.

But what I have not heard is what are the consequences of not implementing the Common Rule because I can tell you that no matter what regulation we come up with, no matter what changes we make to the Common Rule, how are we -- I am assuming that what we want to do is improve the protection of human subjects through increased regulation, not necessarily increase regulation, or to change the regulation, but what are the consequences to the federal agencies or the private organizations that have not implemented the Common Rule?

You know, I would like to hear a little bit more about that because it seems to me that the

consequences do not seem to outweigh the benefits for -- in fact, the people are either ignorant about the Common Rule or just choose not to follow those regulations.

DR. FREEMAN: In the private sector there are some reporting requirements, minimal as they are, and sanctions, minimal as they are. One of the interesting things is that the Federal Government made them part of the implementation of the Common Rule. For the private sector there are nothing, not sanctions, no reporting requirements for how within the Federal Government agencies implement or do not implement the Common Rule. As far as I can tell there are -- except for the report that is about to be issued by NBAC in a few months -- there are no -- I mean, there has been -- there was no structure to do anything of trying to understand whether it is implemented or not, or whatever.

DR. CHILDRESS: Can I just say one thing? Harold and Alta, before you leave if I could just get one thing in.

It seems to me in response to Alta's concern maybe one thing to do would be to see if can get -- given the fact that the interagency Human Subjects Committee -- I do not have the exact title -- met with Bill and others this week and looked over the report, could we ask for feedback not simply about the report but also their

broader concerns since they will be actually continuing to respond -- I have already heard from two of them as a matter of fact -- to respond to us. This would at least give us something to work with and then we can make a further decision about whether to invite groups in.

There is always the open invitation to the public hearings.

DR. MANGEL: It should be clear that we do have data that we did as part of the questionnaire process elicit comments and we asked them what is going on, how do you like it, what is working, what is not working.

MS. CHARO: Right. Some of these Randy had summarized.

DR. MANGEL: Yes. So we do have some data in there. If you want to call them in and ask them, that is fine too, but there is data. There are data already.

MS. CHARO: That is a good reminder.

DR. CHILDRESS: That is important but also it seems to me at this point now having gone through the process and seeing the report, a draft of it, that to go and get some other feedback too.

Thank you both.

DR. FREEMAN: Maybe you, Gary, and we at the office here could work out for the December meeting that --

DR. ELLIS: If you can frame the question with precision I am certain the agencies will do their best to answer whatever question you frame.

NEXT STEPS

DR. CHILDRESS: We will continue to work on it.

We are losing our members as you can see. The exodus has occurred. So let's see if there are any last comments from people and then we will bring it to a close since we are down now to three of us. Arturo, Laurie and myself.

DR. FREEMAN: You mean last comments from us?

DR. CHILDRESS: From you folks, yes.

DR. FREEMAN: I think the more feedback we can get from you folks the better. So I encourage you to do that. What is not clear and so on? This is somewhat of a different report obviously. I mean, we are not talking about thoughts and just ethics and stuff. We are talking about some facts and noncompliance, and it is controversial.

DR. CHILDRESS: Right. I think we are kind of broadening that. Some of the subcommittees are moving towards we will incorporate this into a larger kind of document --

DR. FREEMAN: That is right.

DR. CHILDRESS: -- that will include some of the other sorts of things and I think that is the stage we will be starting on.

DR. FREEMAN: Good.

DR. CHILDRESS: But that means though that your work will still continue.

DR. FREEMAN: Yes.

DR. CHILDRESS: That is to say there is still the flushing out that you folks are working on all the time that will be part of it as well.

DR. FREEMAN: The other thing is there is a question of how -- to help us as well -- how close do you think this is to where it needs to be in timing?

DR. CHILDRESS: Well, as --

DR. FREEMAN: I am not saying we need the answer now but this is --

DR. CHILDRESS: Right. Okay. But I think that we will have Kathi go ahead and start with subcommittee members on recasting and doing the larger and then I think you should provide -- continue to provide the information you can. For example, I am assuming that the descriptive -- the summaries, the data summaries, that we have part of that, the others are in the process of being developed. I am sure that some of the Phase II material, for example, is in the process of being

developed. So all that should continue and we will start the other process as well. Did that make sense?

DR. FREEMAN: Sure.

ADJOURNMENT

DR. CHILDRESS: Well, thank you, Emily, Joel and Bill, and everyone else involved, and we are grateful to you and I thank the subcommittee members for your endurance today. This is becoming a test of endurance for everyone at these meetings but thank you all.

We are adjourned.

(Whereupon, the proceedings were adjourned at 4:15 p.m.)

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