# NATIONAL BIOETHICS ADVISORY COMMISSION

## HUMAN SUBJECTS SUBCOMMITTEE MEETING

**July 15, 1997**

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**Agenda Item: Update and Overview - Dr. James Childress**

Dr. SHAPIRO: Colleagues, excuse me for interrupting. Jim Childress and I were determined to start on time today. We really have a very full agenda so I would ask the commissioners to please assemble.

As you all know, we will be spending today on the work of the Human Subjects Subcommittee which has been pursuing a very ambitious agenda and has an equally ambitious target of having its initial reports out later this year. So let me then turn the chair over to you to take us through today's ambitious agenda. Thank you very much.

DR. CHILDRESS: Thanks, Harold. Welcome, Everyone. This heavy agenda does represent an effort to catch up following our three months on human cloning so as Harold mentioned, we do have a lot to cover. I will try to keep us fairly close to the schedule, especially because I know that several have to catch flights to the West Coast this afternoon. But we need to take the time we need to cover the topics that we have addressed and knowing that we will not be able to cover everything in depth so we will try to find the right balance today.

I wonder if anyone else on the staff, Henrietta,

do you want to say anything about our activities. You are already familiar with members of the staff but let me introduce one who is joining us and is new, Jonathan Marino who is there at the end of the table and Jonathan some of you met when he appeared before the Human Subjects Subcommittee earlier this year. He is director of humanities and medicine at the Center, the Health Sciences Center in Brooklyn, and director of the Human Research Ethics Projects at the University of Pennsylvania Center for Biomedical Ethics and we are glad that he will be working with us half time.

Let me give you a quick overview if you will just glance at the draft agenda. The first part will be devoted to consideration of our projected report on federal agency protection of human subjects, and then the rest of the morning will be spent dealing with research with decisionally impaired or cognitively impaired subjects, and we will have several visitors joining us for those discussions.

And then after lunch we will turn to the proposal that Alex Capron made prior to the Virginia summit meeting which we were obviously unable to consider on lack of data and federal research oversight, and then spend a couple of hours thinking about our projects and priorities, including matters that had been raised before and others that have

come before the subcommittee to try to determine how we can best proceed over the next several months, including getting contract papers on other topics and the like.

Then finally we close with statements by the public, and I would ask those in the public who plan to speak to let staff outside know. That will help us plan that part of the day and second would ask people who are planning to speak to limit their comments to five minutes and then there would be some brief time for discussion with presenters after that.

Any comments about the agenda before we get down to business?

PROF. CAPRON: I had one question. We received material from Dr. Freeman right before this meeting. When are we going to get a chance to discuss it?

DR. CHILDRESS: In the projects and priorities. You are talking about the emergency research?

PROF. CAPRON: Yes.

DR. CHILDRESS: Because what he is raising there, there is a possibility of having some either contract papers or further work on how one does bioethics in public or how one assesses risk so we will talk about it in terms of possible projects. That is also true for another matter that was circulated, having to do with international research. Other points about the agenda?

Okay, having gained five minutes, let's start with our discussion of decisionally impaired subjects. I am sorry, I am jumping ahead on the agenda, trying to gain an hour. Let's start with federal agency protection of human subjects and let me say a few words about that.

As you have heard me say before and this remains true, we are grateful to Bill Freeman, Emily Feinstein and Joel Mangel for the splendid work they are doing on this project. They have been wonderful in every respect in developing the material we need to make a report in this area. But also I would like to express my gratitude to representatives of the federal agencies for their valuable cooperation and underline what sometimes may be overlooked in our pursuit of the extent of compliance with the common rule and that is that we would welcome both to the staff and to the subcommittee directly any reports of creative efforts that go beyond the common rule to try to protect human subjects since this is also part of our interest in the overall protection of human subjects.

So we are interested in compliance but we are also interested in creative ways that that might be shared with others.

We had a conference call in mid-June because we were unable to have the meeting on June 7 to discuss how to proceed with the federal agency report and in the

conference call we felt that it was important to try to, if we could, cover in the limited time we had both phases one and two for the report, that is, deal with both the structure and the process and to get additional staff if necessary.

Our three staff members on the project explored options and we are going to have Jonathan Moreno work with the staff already assigned to this at least a day a week. There will be reassignment of some responsibilities within the invite staff to provide additional help for this project. There are discussions underway with an analyst-writer to work on the draft in August and September and so forth.

The staff feels comfortable, I think, based on our discussion, that they can proceed with this support to produce the drafts. I will let them talk about the scheduled content and the like so let me turn it over to, Bill, are you, and again, thank you very, very much, all of you.

**Agenda Item: Report on Federal Agency Protection of Human Subjects -- Dr. William Freeman, Ms. Emily Feinstein and Mr. Joel Mangel**

DR. FREEMAN: Thank you. I also want to express thanks to all the federal agencies that we have interviewed and those that we will interview for their cooperation.

Some are here. It has been very helpful with that cooperation. You have, there was passed out by mail or Fedex the draft agenda for this 35 minutes, and just to follow that, you have in the packet the final protocol which includes all the background, all that kind of stuff as well as the specific survey forms and the consent form data, final as of the 10th of July.

Most of you have seen prior versions. There is not much change from the prior versions. By the way, interrupt any of us at any time with questions, comments or whatever.

I wanted to go to more what is new for most of you which is the summary outline for NVAC, the implementation of common rule by federal departments and agencies dated the 10th of July and it is in horizontal, not vertical format. It is a table and, just to briefly explain it, the agencies are on the left hand side. The first two columns of substance, the next column, by the way, is just a number, it is a code number for our purposes that we have. The National Commission, the President's Commission are sort of summary of their investigation of federal agencies. The next three columns are just lists of in the President's Commission. The second report, there was mention of an ad hoc committee that basically became the committee to develop the common rule for the entire

Federal Government so it was the agency listed in that.

Then there is the people who signed on or departments who signed on to the common rule, they are listed there and then HSRC, that is what is called the Interagency Committee. They list it on the Interagency Committee which is currently the committee of coordination of implementing the common rule.

The next two columns are the ACHRE, that is Advisory Committee for Human Radiation Experiments. They did a survey very much more limited of some of the Federal Government agencies and departments, what they found, and then in response to the President's executive order, the next column, what was the written response that the President and NDOT received.

The final column is just what dates have we, did we interview these people. There are some lessons that I will just walk you through some of the interesting findings. For instance, if you go down to 10, just go down the second column, the numbers there in numerical order, 1030, you notice that there is a report in the National Commission and then there is nothing further. That is one of the agencies within a department.

One of the things we are finding is that we really have to, in many departments go to each individual agency and ask them specifically what is going on for two

reasons. One is that there is variation among the agencies within the department and therefore the summary overall of what the department might way doesn't really reflect that, the specifics of what is happening.

Some agencies might be just doing intramural research, that is, their employees are doing research, others might be paying for research extramural supported elsewhere. Going down to number 2,000, you notice as you go across, let me just explain how the columns work. On the left hand part of the column is either an "I," an "E," or both intramural or extramural. On the right hand side of the column, and this is explained on the first page, there is an "R" for regulations basically similar to the common rule at the time before the common rule 45 CFR 46, "O" for other regulations at the time, none for none and second I will explain at the end.

But just going to number 2,000, you notice that the first report they have other regulations. The next report they had no regulations. The next report, ACHRE, they had other regulations. This is after 1991 and in the executive order, they are in draft.

The point is that the, when written things are sent out as I believe the National Commission, the President's Commission, ACHRE and the executive order, sent out basically in writing, please tell us what you are

doing, in somewhat detail. I understand at least the President's Commission actually had a detailed set of questions but nevertheless it is in writing and you get back something in writing. It is a great chance for misunderstanding and therefore what we get back may not be reflecting what we understood we were asking for.

Our survey on phase one which is about structure is what is the structure in place for protecting human subjects in intramural research as well as extramural research. It takes about 2.5 to 3 hours and we asked such details, and in a face to face conversation, we make sure that they understand what we are asking and we understand what we are saying so this kind of confusion exemplified in going across the line on 2000 hopefully doesn't happen, at least it doesn't happen as often.

Just to go to the second page on Department 4000, you notice there is very little there, but they are listed in the ad hoc committee, then they are not listed in the common rule and they are not on the interagency committee. There is nothing about whether they do research or not, yet they were in that ad hoc committee.

Again, this is sort of an anomaly and what we will be finding out, this also says something that we are not restricting ourselves to the just interviewing people that are listed in the common rule. This agency is, the

department is not listed in the common rule. I have good reason to understand that they do research and we haven't reviewed them yet.

We are not there, we always say Joel, his opening statement is we are not playing a gotcha game. We are not playing a gotcha game with the people we are interviewing. We are trying to find out what the situation is and if it is something that is not what we would expect, why so that it can be remedied. We don't go in as a Congressional hearing and make people embarrassed and that kind of stuff. So it is not, with I think only one exception, I believe the people that we have interacting with have been comfortable and we have felt comfortable with them. We are in common approach to improve this situation if it needs improving or to pass on pearls that some agencies indeed have very good ways of implementing.

This is another example when you put this table together of where there seems to be some indication of a problem that needs to be looked at in terms of is the department having, doing research, should they be part of the common rule, et cetera.

And then just one other, on the next page which is page four in terms of problems, just look at 6,000 and you will notice what I mentioned before, this variation under 6,000 in the different agencies of what they are

doing and so on. So a summary report from a department is not very helpful. We really do need to go to the agencies in almost every department.

I want to make it a sandwich. You have the top bread which is the complement, you have done that. The middle stuff is some problems and then end with another complement and the complement is on page five. I mentioned that second 2-ND. That means there is second review by this particular agency in terms of, for instance, extramural research that their own IRB reviews the, what the extramural IRB has reviewed and/or that there is second review of intramural research. In other words, a second higher level IRB reviews everything and there are second and earlier pages, but just in five, you can see that actually there were two there as well.

So that some agencies have gone beyond the common rule in terms of their efforts to protect human subjects and that is also important.

PROF. CAPRON: One of the ways in the chart has a lot of blank space is the many particularly for the Department of Health and Human Services, the many sub-units that are listed separately. Some of those are in italics and it means you are only going to be looking at them in phase two.

DR. FREEMAN: That is correct.

PROF. CAPRON: But many of the others are listed and I wondered, is it your expectation that when this material is published it will be published in the same format because I would be concerned that someone looking at this quickly would see all these blanks and would be concerned that somehow large parts of the Federal Government are unresponsive to this when, in fact, there is no reason for the Administration on Aging to have a separate set of regulations from HHS, et cetera, et cetera. Have you given thought to that?

DR. FREEMAN: Yes, this is a summary and you are absolutely correct that the reason for the large blanks is that, especially the sub-sub agencies were not part of the surveys directly of the other prior reports. Some of the ones that are not in italics we will, in fact, do a phase two survey on but we are doing a phase one. The reason you have there the phase two is that we are going, the phase two survey is a process, more of a process survey, where we go to the chair of the IRB and the, for instance, NIH as a whole does not have an IRB. They have an office so we have to go to the next lower level to look at what is a process that IRB is having. We just did one Friday. It is a three hour survey and we found that actually some of the questions we had to leave out and we decided which were the unimportant ones in your phase two questionnaire that is in

the protocol.

The report will be structured in a way that I don't think there is going to be that confusion. I would expect that there is going to be a chapter on phase one and it will be in prose and about themes. We will probably have the agency-specific data, unlike, say, the prior commissions where there is a lot of prose in each agency. It will probably be in tabular format.

We have been talking, the staff and Dr. Childress, more interested in patterns and themes and although specific departments may be mentioned in that chapter, most of the agency-specific and department-specific things will be in a tabular format, at, say an appendix or something like that.

PROF. CAPRON: But even in the appendix, I mean, for example, I am just not quite clear if I follow your whole answer. Does the Assistant Secretary for Planning and Evaluation have a separate IRB? Is that why that office is listed?

DR. FREEMAN: We don't know that.

PROF. CAPRON: If it is listed, it has no date on it.

DR. FREEMAN: That is correct. We have not interviewed them yet. That is why we don't know what is the situation. We understand that they may be doing

research but we need to find out.

PROF. CAPRON: I see. You understand that just by the common assumption that something that is called planing and evaluation would have some research component?

DR. FREEMAN: That and as a federal bureaucrat dealing with research myself, I have had experience with various other departments and agencies and HHS.

DR. EMANUEL: But I would emphasize what Alex says. For example, AHCPR is listed. They didn't even exist when the National Commission, and so there is some deception just in the table. If you don't put an X through the box, people don't know that they couldn't have even had a category there because they weren't in existence. So I think there is some sense here that maybe black out the box where either they weren't surveyed and so you didn't have the data or they didn't exist and I think that would help, Alex is right. Some cursory person looking and saying wow, there are a lot of places out of compliance or were out of compliance.

DR. FREEMAN: By the way, I am not sure that this table is going to go in the final report.

PROF. CAPRON: I understand that and that is one of the reasons I was asking what your plans are. I think tabular presentation of information is very useful. The President's Commission did that as well as well as well

written prose about it drawing out the themes. I think your approach is absolutely right. I just want to be sensitive, once this document takes on a life of its own in a printed report that we have thought through what interpretations can be drawn from the fact that someone was listed.

DR. FREEMAN: Right, this is, I guess I don't know what proper phases a working document for you for information, this is not an initial draft of our report.

PROF. CAPRON: This is, in effect, telling us this is what the staff is looking at and if one of us looked at it and said why haven't you listed it, this would be a good way of knowing what you are doing.

One other question if I might, the interior department, you drew our attention to the interior department at 4000, and I expected to see under the executive order, something, because the page, the key on the cover page, said or for interior, response to Emily Feinstein's letter asking for the name of the person appointed to work with NVAC. Does that indicate you have received no response to that letter?

DR. FREEMAN: Actually, I think that is a mistake in the table because there should have been then no research under executive order.

PROF. CAPRON: But you have reason to think, for

example, that the Bureau of Indian Affairs does research?

DR. FREEMAN: I have reason to believe that.

PROF. CAPRON: So that is a response, you also don't have an interview data set. Is that right?

DR. FREEMAN: These are past interview dates. We don't put in a date until we have them because they get canceled and that kind of stuff. We are working on dates here.

PROF. CAPRON: Okay, good, thank you.

DR. MIIKE: Just for my report, last night I was telling Siecke(?) Bill Freeman and I graduated from Amherst 13 years ahead of him. There is Agency for Health Care Policy and Research. It is called the National Center for Health Services. Before that it was the National Center for Health Services Research and Development. So somebody is thinking of these name changes.

DR. FREEMAN: I am using the current name in all of these but your point is, it was, they were not even asked if they were a sub-sub agency. I think they got elevated.

DR. CHILDRESS: I have a point about the schedule and so forth.

DR. FREEMAN: Okay, we have got, what is not on the agenda just a brief report from Joel about a summary of what we are finding just to let you know that we are

thinking about what we are doing although we are still in the process of analyzing the data.

MR. MANGEL: Is this turned on? Yes. When we first met, early on, and were responding to the written responses that we got from the agencies, my conclusion was that there was great unevenness. Now that we have met with most of the agencies, I would have to say that that impression has been intensified.

The thing that impresses us and me, and I have been in the government for 30 years, is just how much stuff the Federal Government is doing and how many combinations and variations of organizations there are so that unevenness I guess is to be expected.

Now, some of the areas that we have found unevenness in, and I am not going to be specific because we are still getting reports and we told the agencies we will show them what our conclusions are before we publish them and give them an opportunity to talk so I am going to be as unspecific as I can be.

We have found unevenness, for example, in the way they construe the regulations and in particular the exemptions. And some of the agencies are construing exemptions in ways in which I think would be very favorable to them and others are construing exemptions the way, in ways that might restrict them.

Another area that we are finding unevenness is in the vigor with which some of the agencies are enforcing the regulations and that often, though not always, relates to just how typically their research is biomedical or behavioral. There seems to be something about that that focuses the attention and, again, that may not be unusual.

Another thing that I think we see is a variation in the amount of personnel and organizational identity that the agencies are giving so that in some agencies there will be a specific person or office that has got a function and then quite naturally those are the agencies where we will see some more not only vigorous enforcement but more personnel devoted, and then, of course, also we are seeing a great deal of diversity in sophistication and once again that often relates to just how typical the kind of research they are doing.

So I think that the byword is a great range of reactions of the federal agencies.

DR. EMANUEL: A great range can be above a floor or it can encompass the floor and the basement.

MR. MANGEL: Yes, it can.

DR. EMANUEL: Can you just give us an impression?

MR. MANGEL: Well, I am really going to be evasive or reluctant because we haven't given the agencies really a fair chance. Now, I would say that if one were to

look at the bulk of the research that is being conducted by the Federal Government, the conclusion would be that there has been serious attention given. If one were to look at the full range of the agencies, one would be a little concerned.

DR. FREEMAN: But most of the research is conducted by three groups, by Health and Human Services, Department of Defense and Department of Energy so there is the regulation is much less.

MR. MANGEL: Now, of course, because of the lack of real, our ability to look at large numbers of specific projects, we can't say for sure that this agency is doing or not doing a lot of research but the impression we have is that the major research agencies are paying serious debts.

DR. CHILDRESS: Other questions? Alex.

PROF. CAPRON: This is a question that relates to the scope of what you are looking at, Joel and Bill. It was in part prompted by your comment reminding us of medical or biomedical and behavioral as the focus for some of the work. Between biomedical and behavioral there is a long tradition of greater discomfort in the behavioral community with all research regulations and it would be helpful, I am not asking for comment now, but I just want to know if your process is likely to put you in the

position to give us comment later, to know the extent to which that remains a problem in the sense that it is either harder for agencies to effectively use regulations in that area, in the behavioral area or that agencies that do a lot of work in that area have a less, uh, strict I think was your word, interpretation of the rules and the exemptions.

Then there is a third level which is social policy experiments and we know that there is a special ruling about such social policy experiments. Because of that ruling, does that mean that in your -- this is a two-part question -- does that mean that you are not likely to be looking at the partners or agencies that sponsor social policy experiments?

DR. FREEMAN: We are looking at every department and agency including those that considered their research exempt on any basis. There are other exemptions and that we might even agree with before or after the interview. There are questions of who determines is that a categorical exemption or is each project looked at individually. What is, in fact, the nature of the exemption? The exemption can be broad or narrow. For instance, just taking the social policy one, does it apply simply to doing the randomization, let's take the one that really promoted, I don't know that much about it but dealing with the Social Security experiment, I think on something different --

PROF. CAPRON: Housing subsidies I think it was.

DR. FREEMAN: Okay. And so they randomly allocate people to different or communities to different ways of subsidizing housing. It can be that the exemption is narrow and says that is all we are doing but we get consent from each individual if we ask them questions to evaluate that or it is broader and says well, that is part of the experiment and therefore that also is exempt so we have to find out the details about what that is. That is your second question. We are going to every one and trying to get details. We will expect to make a report. In our report we will make some statements about possible problems about that exemption in terms of the things I just mentioned -- how broad, how narrow, might it be and what are the consequences when it is broad or narrow.

PROF. CAPRON: The first question was are we going to get similarly nuanced responses on the biomedical and behavioral side and particularly what I would bring to this which would be concern that the behavioral side has had, that the impulse towards greater leeway there may lead to interpretations that we ought to be at least aware of.

DR. FREEMAN: We are paying attention to that, we have seen that as an area of discussion. You notice I don't necessarily say problem. There are two really parts to your, to the answer. One is, yes it is an area of

discussion. It is a subset of a larger area, something you didn't raise which is are there problems in actually implementing the common rule as is. That can also have to do with size. If you have an entire agency that pays for supposed 10 human subjects for protocols a year extramurally, what is the mechanism in place that would be effective with skills people to analyze that eight of them that have their IRB, two of them don't have an MPA IRB and therefore staff have to review it.

If you have staff reviewing protocols, two a year, that is going to be difficult to maintain skills. So there are practical issues that we are coming up with as we ask the agencies. We are not going in and saying the common rule is the decalogue from, on cyanide and we all must observe it. We are trying to find out what are the practical issues involved.

DR. MIIKE: Just a follow up on that. In your look at these agencies, are you coming to any conclusion about the appropriateness of the common rule, both as it is written and as it applies to specific agencies? Are you coming across instances where it is more just sort of a paper kind of a thing with really no real consequence, one way or the other in terms of the actual experiments themselves. Is, I know you are trying to reach across all federal agencies but the secondary question to me is that

must it reach across all federal agencies and must it reach everything that could possibly come under that umbrella?

DR. FREEMAN: I put it not that we are coming to conclusions but we are getting information about that for you to make your conclusions, the commission and we will be giving information about that. It is partly related to what I just said which probably triggered your question of this -- how does it work in small agencies or agencies that do small amounts of research. We will be looking at your general question. I think, however, the paperwork exercise that is just a paperwork exercise question is more likely to be answered in phase two and possibly this is too early to say for sure but it has been mentioned among you all perhaps a phase three of actually going and watching IRBs and actually going to the meetings and interviewing people.

In other words, phase two is a process. It is a process but it is still not watching what happens. And do these reviews make a difference in terms of the protocols.

DR. MIIKE: In terms of agencies that have one or two research topics. They may be very significant research that needs to be overseen. I am just more concerned about the ones that sort of hit you in the gut and it is like, well, yes, it falls within the definition but it doesn't really make any difference. Not that there are differences like that but I would guess there are.

DR. FREEMAN: There are. I think the, and we have seen some of that. I am not sure we have seen that 100 percent of the research that they need to do or support fits in that category so you have got a situation most of the time where agencies are doing very low risk research or those that do bring low risk research once in a while still will have something that can be higher risk and how does the agency differentiate.

DR. CHILDRESS: We will take one more question and then turn to the plan for finishing the report.

DR. EMANUEL: I am quite interested in the fact that some agencies go beyond the common rule, and I want to ask two questions about it because it intrigues me. One is, what is their motivation. Why did anyone think to do this because it might create some idea for us about what kind of incentives might be in place to actually take this seriously and do more. The second is could you give us some sense as to what go beyond the common rule is, in some instances without naming particulars or what you think are appropriate.

DR. FREEMAN: Again, the most common going beyond is the second level review. Either within the agency or research that they support outside and that the university has their IRB. One of the things we have found is on the ladder that it is not a paper exercise, that they come up

with substantively, some of them come up with substantively different or additional concerns that they feed back.

There are patterns, at one time I thought it was agencies that had to do with safety. That turns out not to be a pattern because other agencies that have to do with safety don't. So it appears one common pattern is perhaps an accident of, unfortunately, an accident of history where you have from the beginning people in that agency that just don't believe in it and are compulsive about it and from the beginning, and we can see on that page five, from the beginning, two of the agencies, 9550 and 9560, were going beyond what is now the common rule. That is one pattern that we have seen.

Another pattern of not necessarily going beyond the common rule but certainly getting it together is scandal. That is unfortunate but that is the way it is, the scandal being that there was a, something inappropriate about, some inappropriate research that got into the public press and they said we need to tighten up. Often then when they tighten up, they do a very good job. Going beyond the common rule in the sense of things like training researchers to understand, especially in very logical organizations, to understand what the common rule is because that is the first line of defense, after all, is that all researchers do what they are supposed to do which

is to submit research, don't just go into the freezer next door with the specimens and take it out and do your thing. But go through a process of protocol and review.

That is, now that I think of it, another going beyond, paying a lot of attention to educating researchers and the entire organization of what to do.

MR. MANGEL: Another case of going beyond at least with one agency was a case where the agency felt that the nature of the research it was doing was so cutting edge and so sophisticated that it thought that it possessed a unique ability and so they wanted to apply that to the judgments of another IRB.

DR. FREEMAN: Actually, that brings up another one of where the research, that and the one I am mentioning are a special kind of thing but where the research subjects were in such a peculiar situation, peculiar in a good sense that they had to go beyond the regulations in terms of protecting them and involving them in research.

DR. EMANUEL: I was hoping you would actually give us a different answer for the incentive structure because it is just scandal which we don't want to repeat and it is very energetic and committed individuals that makes it hard to create a systematic incentive.

DR. MORENO: It is not only scandal, it is a certain kind of scandal. Two of the three agencies for the

advisory committee, CIA and DOD that level of review directly related to psychoactive drug studies that were reviewed in the mid-1970s so maybe we should have all the agencies try all these and publicize it.

DR. CHILDRESS: Okay, last question.

DR. SHAPIRO: Just one comment. I just want to endorse Alice's comments on, various comments on the behavioral issues. That is a theme that is out there unresolved and it keeps popping up and no one deals with it in a straightforward way as far as I can tell so I really want to just second the comments that I think are quite important if we can say something useful.

DR. CHILDRESS: All right. I had planned for finishing this up. Do you want to talk about it or should I?

MS. FEINSTEIN: I will talk about it a little bit and re-evaluate it and then we can use our resources because we can change the shape of our protocol and what we want to put into the report in the timeline that we have allotted. The first important thing is in addition to being staff to the project, the phase one interviews, Joel and I are probably going to take over and finish by beginning of August and we are going to phase in other staff members that have been supporting the genetic subcommittee and that includes Sean Sumner and Rob Tanner

and they are going to phase into phase two with the help of Jonathan Moreno and, of course, Dr. Bill Freeman, so they can finish the phase two concurrently.

We are also looking to hire a writer to help us write out and begin, hopefully before we finish the interviewing process and do the background and the research. When I finish the interviews, I will help collating the data and bringing the writer up to speed with that so that we can have a preliminary draft to you by maybe mid-August to start reviewing and working towards our timeline of October. I think Bill is going to talk a bit about the process of doing drafts.

DR. FREEMAN: You have as a handout this, dated the 11th of July worklist. This is not a schedule. It just lists the, in phase one of, with our new plans, the ones that we have to begin and we see some dates that have already occurred or are scheduled to occur. You can see it is a significant workplan on the first page.

The second half of the first page is just where you either check or follow up on some questions that we have. This is our own internal document that we just are sharing with you and then the phase two in italics is up on the top of the second page, and you can see there the reason why we picked phase two, the specific groups for phase two and there is some significant issues on genetics,

for instance, on use of large data sets for the anonymity, on variation, possible variation in large organizations and down at the very bottom of page two, I am hoping all of those will be resolved by telephone and it will not add to our worklist appreciably but we have to find out are these possible places that do research.

What we are intending to do is, again, go beyond the charge if we are going to be talking about variation in the federal government, we want to make sure we have surveyed about as everything we can to determine the presence and the type of structure that there is to protect human subjects and that would be independent.

To go over the process of reporting and feedback just in a little more detail, we are hoping to have the medical writer on board very soon. That person can do the background or history chapter based on this table. It should be short. We are aiming for a report of 50 pages or less and I see basically four chapters, depending on how you respond. This is all drafts and for comments, a very brief background of the reports up to now, chapter phase one, phase two, conclusions and recommendations.

We expect to have the background chapter in phase one to you as Emily said in mid-August for feedback, get your feedback from you and have a new one out to you before the September meeting. That may also be the case with

phase two chapters. It depends on how soon we can come to conclusions about phase two. We will have very preliminary draft, I think, for report and recommendations, conclusions and recommendations for you before the September meeting. The first three chapters present data that is more our bailiwick, conclusions and recommendations is clearly your bailiwick, and we will be offering a smorgasbord of options for you to pick and choose and make your own conclusions if we have concluded them.

DR. CHILDRESS: And, Bill, would be, after we reviewed the draft in September as part of the draft goes, to work on that and perhaps have a meeting, if at all possible, with NBAC as a whole in October and finish the report by the end of the month. That is the tentative plan. Harold and staff were working on trying to see what timeline might be possible for an October meeting. Any last questions or comments for staff?

DR. FREEMAN: We have got another item on the agenda. Zeke has mentioned the question about incentives and so on and in our conference call mentioned that whether we want to or you want to do anything about the process of implementing complex regulations and then incredibly complex organization, namely the Federal Government. The Federal Government is basically made up of fiefdoms and then sub-fiefdoms and then probably, we don't know yet, but

even sub-sub fiefdoms but at least it is very clear to us that fiefdoms are the departments and the sub-fiefdoms are the agencies with varying interest and incentives and all that. It seemed pretty clear that regulations don't self-implement.

So the question is, if that is one of the things that we find, to what extent, if any, does NBAC want to talk about how to implement regulations better, that process of implementation. I am not aware that any of the staff at least have any expertise other than our own seat of the pants which is, that has been part of the problem I would guess and the rest of the Federal Government as well, any special expertise about that.

We could, as a range, just mention it in the report and expect the Federal Government to respond appropriately, perhaps to commission papers about it or some variation of that.

DR. CHILDRESS: Any quick response to that?

PROF. CAPRON: When we talked about this before, I suggested that it might be possible to talk to some people at the administrative conference about their experience with regulations. It certainly is true that these periodic commissions of those of us outside the Federal Government who come in and look at these, come up with recommendations and conclusions and sometimes were

around long enough to see if even any action is taken on the recommendation, sometimes we are not event around that long and it becomes just part of the community's awareness that these recommendations have been made but not much has happened, is a pattern which I don't think we ought to fall into now that we have seen it so many times but I don't have a magic solution for it but in terms of a consultant's paper, someone from the administrative conference might.

DR. CHILDRESS: Shall we pursue that possibility then?

DR. SHAPIRO: It seems to me there is a very interesting and even some cases quite obvious things to study, namely recommendations that go into a system with an ongoing regulatory framework to implement and those that don't have such systems. One could study very easily which ones are affected. Not easily, necessarily, but at lest straightforward conceptually to look at it and that might provide a good handle for looking at some of these things and of course, one of the things that differentiates the kind of work we are doing and our predecessors have done is it is very periodic, that is, it comes and goes and we can compare that to other countries where there are standing bodies that deal with this and whether that has any influence or not on this issue I just don't know. One could study it, and I think there are interesting and

viable topics to study.

DR. CHILDRESS: And Harold indicated yesterday that we have funds for conduct papers, if this is one where it would be useful to have one then we ought to pursue that possibility immediately.

PROF. CAPRON: I have been told that the administrative conference has been de-funded.

DR. COX: This issue strikes me as an extremely important one. We can say whatever we want, and if no one knows how to implement it, then it is all a waste of time. So also there has been extensive discussion about how put-upon IRBs are and how they don't know what is going on so this is, although everyone is working extremely hard in IRBs and there is different types of IRBs, it is quite a broad area and I think it would be difficult to be comprehensive but I would be very interested in seeing at least a stab at it because otherwise it is like we are not being serious.

DR. CHILDRESS: And one part of that implementation, in terms of IRBs we are going to talk about this afternoon, the IRB studies that are going on and what we might want to add to it and so if we think about this discussion in terms of the federal agencies and their response, how do they themselves try to bring about change.

MR. MANGEL: My recollection is that the first of

these commissions, the national commission had as part of its legislation a requirement that every federal agency respond within I think it was 90 days and give an explanation of why it did not adopt the recommendation.

PROF. CAPRON: The President's commission did adopt.

MR. MANGEL: Did it? In the national commission case I think that did have some positive effect.

DR. FREEMAN: Jonathan and I just mentioned, we were talking about James Q. Wilson has written a book called Bureaucracy. I have read it. It is not directly applicable. I couldn't get things about implementing regulations, especially in this setting, directly out of it but one question would be whether he or somebody he would recommend might be a good consultant for the paper. It is a big book and it is a summary of just about every chronicle or study that has ever been written about bureaucracy.

PROF. CAPRON: I should note just for the record that passing around a box of salt water taffy interferes with the First Amendment rights.

DR. COX: One other coda on this, I was really struck by your example of the small agencies that don't have much research and how it is difficult to have, perhaps difficult to do the reviews. Again, parts about

implementation with respect to diversity of the federal agencies I think will have a lot to say about the diversity of the private sector if we end up dealing with that issue so I think that there is lots to be said for the exceptions because that is what we are going to be hearing about, about why it is not possible to do it.

DR. FREEMAN: Just one last comment, not on the agenda. You all got the, a subset of the Canadian code, proposed Canadian code, Jerry Alpert mentioned it yesterday. I went, since I have been looking for it with my Canadian colleagues, kept on asking, when is it out, didn't know it was already on the web. I have the entire thing downloaded or printed at the office but the introductory sections of some observations about science in the current setting and then their principles and then the few things that were talked about yesterday, collectives, a big section, section 13 on that, there was a lot of controversy in prior drafts. I happen to know. I looked at it last night. It does not seem to have changed appreciably. I don't have the original but it looks pretty much the same and then genetics and human specimens, not taking the tactic that you did but it did seem that there might be some things that you want to look at.

If anyone wants to either download it, the way to do it is at the bottom of the first section, is type that

in and then you can download the first section and then you see a crunch of one. Don't go to the first page. It doesn't take you anywhere and if you can't do that and you want a particular section, we have got it in the office and we can send it to you.

DR. CHILDRESS: Thanks, Bill, and thank you very much, Bill Emerson and Joel and we are very sorry if this schedule means you won't get a vacation this summer but thank you for everything you are doing on this.

Also, I hope you will be providing a schedule of the phase two at least by e-mail so any commissioners, whether a member of the subcommittee or not might have an opportunity at the time to participate in one of the reviews.

DR. FREEMAN: Or also phase one.

DR. CHILDRESS: There is a few phase ones that are left, too. So if you could provide that maybe later this week by e-mail that would be great and again, thanks very much.

Okay, any last points to be made about that? We are now already a little behind schedule but we are going to turn to the topic that will occupy our attention for the rest of the morning, one that we already paid some attention to in previous meetings and thought we had some momentum on prior to the delays created by our experiment

with Dolly and so now we want to return to our discussion of decision impaired subjects.

You will recall that many months ago, our subcommittee and NBAC as a whole gave this topic a high priority, in part because of the need felt on the part of researchers, patients and families and the broader community in part because this is a widely discussed topic. A number of articles that appeared even in the last several months addressing aspects of the ethics surrounding research with decision impaired subjects, a well-defined positions, indeed a great deal of debate, vigorous debate, about what directions might be taken and there was a feeling on the part of this subcommittee that as we need to protect impaired subjects and perhaps have special guidelines for them and we also need to protect research, valuable research in this area.

So the big question we have to face in thinking about a report and recommendations, we have to find the balance between these two very important interests.

In addition, this has been important for our subcommittee and for NBAC as a whole because several NBAC members have special expertise. Laurie Flynn, who unfortunately is not with us today has obviously a special interest in this area and her testimony on the issues concerning informed consent, protection of human subjects

in research, was circulated in May along with several other statements before one of the I guess Congressional subcommittees. I hope that wasn't lost in all the material we had at that time.

And then for today, Trish Backlar's paper on advance directives was also circulating and then several on the commission of an interest in children obviously are thinking about the ways in which their knowledges between the kinds of protections for children and some of the kinds of issues, by no means all, but some of the kinds of issues that pop up in discussions of decisionally impaired subjects.

Now, in our previous meetings we have heard from individuals, both invited and volunteering to present information in testimony and one of the things we did, even as we were working on the cloning report was to ask Rebecca Dresser who appeared before us to prepare a contract paper and I know that many of you have had a chance to read that very valuable paper. For those who did not meet Rebecca Dresser before, she holds the main chair in the School of Law at Case Western Reserve University and is also a professor at the Center for Biomedical Ethics and we are glad that she could join us.

Also, as you recall, Jonathan Moreno has a special interest in this particular area and expertise as

well so as we will talk later, the plan for developing a report would be to involve Jonathan as a member of the staff and going along and using the extended paper and we really are grateful to you for that extended analysis, Rebecca, in developing the report. I am glad you could join us today.

So what we are going to do in a few minutes here is a couple of things.

One is to ask Rebecca any questions or pose any issues, Rebecca, that you hope might be addressed in a slightly revised version. We don't want this to be a process forever but there maybe, since this was completed now several weeks ago, some things that people would like to see addressed if possible, but then also substantively whether there are issues to get out in discussion with Rebecca that would be important for our own deliberations as a group and knowing that later we will have a discussion with several researchers and others involved with dealing with cognitively impaired subjects.

Rebecca, anything you would like to say to start?

**Agenda Item: Research with Decisionally Impaired Subjects - Drs. Rebecca Dresser and Jonathan Moreno**

DR. DRESSER: Well, I hope you got the sense I think this is a very complicated area. There are lots of concepts and issues to address. I tried to break them down

into the basic questions that I see which I could go through again if you would like.

The other thing I thought you might be interested in is the TD case going on in New York. There has been a recent development in that I thought you might want to know about. The plaintiffs who prevailed and were successful in getting the state regulations struck down appealed to the Court of Appeals of New York which is the highest Court there. The plaintiff, the winners, the defendants did not appeal, the plaintiffs appealed, asking that the decision be extended to both federally funded research and to therapeutic research. The original decision only applied to non-federally funded, non-therapeutic, greater than minimal risk research.

So this probably won't come out until next spring or something but there is a New York committee formed by the Department of Health that is trying to respond to this that Jonathan and I are both on so that is ongoing.

And it is a complicated decision but basically I think the New York rules are certainly, if anything, more stringent and careful than current federal policy governing this population, that is, at least they have specific provisions on assessing capacity and who should do it and risk-benefit ratios and so forth which really are non-existent in the federal policy and the TD decision that

exists now said that the state rules may be unconstitutional and suggested that there are constitutional issues with these New York rules which I think the implication is that this court may find constitutional issues with the federal policy.

I am not sure what the jurisdictional aspects of that are but anyway I think it is a challenge to pay attention to that will be going on while you all are doing your deliberations.

DR. CHILDRESS: And since you mentioned the New York commission, Rebecca had asked if it would be possible to share this paper with the New York commission and my assumption was that there wouldn't be a problem but let me run that by you since this at some point will become a public document, it does contribute to the, significantly I think to the public discussion of these matters so is there any objection to that?

DR. DRESSER: Thank you.

DR. CHILDRESS: All right, it is open for a discussion with Rebecca and Jonathan, also, you have a lecture that he gave at a conference that we both participated in at the University of Maryland on decision impaired subjects and that appears on the packet as well and I think from both of these, we have a bulk of materials that can really be used in a report.

PROF. CAPRON: Rebecca, I just wanted clarification on the TD case. My understanding was that the basis for that further claim as to federally sponsored research was that back at the time when the New York regulations were first implemented, they were operating on the assumption that somehow federally funded research was well reviewed and that what they had found in New York because the federal regulations never were implemented for this area is that that is not the case and that is the claim they are making in trying to substantiate it. Is that correct?

DR. DRESSER: The plaintiffs in their brief to the Court of Appeals, I haven't seen that brief so I am not sure.

PROF. CAPRON: I think it would be very valuable for us to get a copy of that brief and for Jonathan or you or whoever is going to be helping us on that to look there because given the kind of work that the plaintiffs and their amicae have done in the past on this case, it is fairly detailed and I would suspect that, and of course, in the first case the court agreed is what they were saying. I would expect that to be a valuable resource for us in examining the issue more broadly because it has application beyond New York to any other situation.

DR. DRESSER: I did talk with one of the main

lawyers and I think that their arguments were that the federal regulations themselves give states leeway to be more restrictive on research than the federal policy is and then secondly they said they didn't see why greater than minimal risk research offering the possibility of direct benefit was any less of concern than greater than minimal risk research that does not offer a benefit so they just saw the risk of it as important.

DR. MORENO: The whole issue of so-called therapeutic research has been one of the central questions that has gone back to the national commission that has bedeviled the field and I think particularly the context of medication withdrawal protocols where the argument is made that there are unacceptable side effects from present medications and so forth, and then a different regimen or a different approach is being suggested. The whole notion of what amounts to therapy, what amounts to benefit is so complex. It is not obviously restricted to research for the mentally impaired or research on mental illness but in some ways it becomes particularly acute in that area and again just as there are topics which we have to examine in and of themselves, in this case the mental incapacity question, they may lead us into broader topics that we really ought to highlight for our further deliberation and not restrict it to the mental incapacity.

PROF. CAPRON: Can I just add to that a second? I am treading carefully this morning because Jim told me I should take an active but secondary role as staff and so on. As a philosopher in a medical school, I am accustomed to precisely that. With respect to the nature of the brief in New York which was a long time in developing, their concerns were rather more technical as you might expect. For example, they objected to the alleged violation of a statute in New York with respect to the authority that the Department of Health had to transfer.

DR. MORENO: Yes, but that is the first one but this is the second.

PROF. CAPRON: Oh, you want the appeal.

DR. MORENO: This new claim which in effect said, as you said, the first claim was there should have been a commissioner of health instead of the commissioner of mental health and it is what is the status now with this new claim that even within that structure which the New York statute established. The New York statute, it wasn't regulation, the New York statute said you have got the federally supervised, we won't get into that because that has all the federal protections. We want to insure that non-federally funded research has the federal protections so they went on that, the regulations implementing the non-federal were from the wrong agency, from somebody who was

too closely connected with mental health, it was the commissioner of health who should have been doing it. He would have had broader concerns.

And now they are saying, as I understand it, wait a second, federal protection, what about the federal protections. And if they have substantiation, because they have dealt with the details of the way research was carried, I mean, they aren't just making global, as I recall what I have done, they are saying specifically there have been these instances of harm and if they are now saying, and the federal regulations either or apply there and didn't do any good or don't do any good generally. I would like to know what their claims are and I would like to have you all analyze that for us and say, is there anything that is useful there, not because we want to become enmeshed in the TD case but as a broader indication of the kinds of problems which are relevant to our commission.

DR. DRESSER: My understanding is all it was so far is just a petition for the higher court to hear the case and the briefs won't be submitted until sometime this fall.

PROF. CAPRON: You are on top of it so that is very helpful.

DR. CHILDRESS: Let me pose a just a general

question that seems to me to be important for the way we frame the issues and our discussion also in our report. The language varies so much here. We talk about decisionally impaired subjects, cognitively impaired, cognitively incapable, minimally disabled. All those are terms that are used and sometimes they are used interchangeably but they would capture different populations in different ways, would point to obviously something broader and something narrower in terms of the kind of limitation or impairment that is focused on. Any thoughts about that, that you chose for your report, the decisionally incapable, is that the main one you used?

DR. DRESSER: I think I switched around. I said mental disability. One comment I got about the terms is that when you say cognitive impairment, it might not encompass people who have an affective disorder or problem that might get in the way of their ability to make decisions so that is why I tend to use that term more but I agree with you that the terms are used sort of interchangeably. I think, of course, decisionally incapable I think is more precise. I mean, that is saying there is this subset of the greater population that in some way you would believe are not able to engage themselves.

DR. CHILDRESS: Incapable which takes it farther than impaired.

DR. DRESSER: Decisionally impaired. Well, I think that illustrates we are talking about gradations and continuum and that is one of the complexities here. You have got people who are, just in general people are so variable in how, we are all variable in how we make decisions but when you have this population, it is not as though there are some who are clearly capable of making decisions that everybody else does and some who are clearly not and we have also got all the people in between.

DR. CHILDRESS: This is something for us to think about. Harold, and then we will get just a few other comments and suggestions for Rebecca about any revisions we would like for her to make in what is already a very fine paper.

DR. SHAPIRO: This last set of interchanges is a focus on areas that has been sort of twirling around in the back of my mind not knowing how to deal with it, and that is deciding who is in this population, however it is described and who is out and where that decision gets made and if you actually need a process for that in your judgment as opposed to just saying everybody decides on their own who is in and who is out. And I would just would like for those of you who have more experience here than I in this particular area, how you really see or might imagine implementing some different set of standards

somehow articulated in this case. How would that, on an ongoing basis be decided. That is, whether this subject, the population you are studying, or you wish to involve in your research, is in this category or not in this category, however that category is defined.

Is that a tough issue, is that a simple issue for people who have thought about it carefully?

DR. DRESSER: You know, I don't think there is much discussion in the literature about that. I think there may be kind of an implied judgment that anybody with a diagnosis of, say, dementia or a psychiatric disorder, you might want to be especially concerned about assessing capacity initially but of course we want all subjects who make decisions to enter research to be capable and to some extent the disclosure of information process and the discussion with investigators ought to pick up on subjects in other kinds of research, say on heart research or something who might not be capable of making decisions to enter the study and you are going to have people like that.

But yes, it probably would be good to have a definition in any kind of a set of regulations or discuss this issue in the report. How do we want to sort of trigger the special protections or the special procedures that would be applied to look at capacity in these populations.

DR. SHAPIRO: For those who are thinking about this more carefully, one does need to, might want to at least think about having some recommendations that deal with it in a process sense so that this, and there is a process by which a researcher might make a proposal viewed and someone else sort of, just as we talked about yesterday in the scheme that Zeke had up on the screen where the IRB's role, if I understood it from your proposal, Zeke, was to sort of see has the investigator got this right and has he categorized in this case the population correctly and if so, you might want to think about a process analogous to that although designed for this purpose. I am sorry, I interrupted you.

DR. DRESSER: No, no, I was going to interrupt you. Actually, I don't mean, I think that this is a discussion that we might want to broach when Dr. Appelbaum is here because his particular expertise is blit(?) capacity and I think he might have a lot of ideas to give us and in a sense, I would like to sort of table that discussion if that is all right with you.

DR. CHILDRESS: That makes sense. Zeke?

DR. EMANUEL: I just want to raise two issues. One is whether clumping all these categories, all these people into one category is the right thing. It has always made me a little nervous, to be quite frank. I don't like

the broad rubric, decisionally incapacitated or any of the others that you are mentioning, probably because it seems to me mental illness that is of an effective kind versus dementia, maybe one rule is not going to work. That is my own, and I have to say that is a bit uneducated. I have not thought deeply about this to any level that you or Jonathan had.

And the other is in the current environment, where we have just had several scandals, I am always worried about scandals tipping the balance of consideration to avoidance of risk with the potential for benefit getting shortchanged. That is just a sort of general comment and in the current, whenever you review research, there is always this problem, how do you estimate benefit, especially since you had no way of knowing what effect, I mean, part of the reason for doing the research is usually to determine the effectiveness of your intervention. This is more than just a question, I mean, this is not a question but it is just a concern to the commission that when we consider this, I think the way of trying to make sure we have the balance and risk ratio correctly calibrated, especially since we are all concerned when you have got people who are killing themselves, you have got to be very concerned that the risks are well taken care of but similarly, the benefits, especially with a large, growing

dementia population I think need to be very well taken account of and I am not sure exactly how to do that.

DR. MORENO: Can I just say something in review of the problem. It is interesting to reflect that the national commission had no way an easier time because they were talking about those institutionalized as mentally infirm and I am skeptical instruction. And in the 1970s, of course, following Attica and so forth, we were especially concerned about institutions, total institutions and so forth. The bottom line, of course, was the institutionalization was happening while they were writing the report. The recommendations wouldn't probably have had much bite in that respect anyway.

Our problem is really much worse because we don't have an obvious sort of delimited way of categorizing this thing. I think I want to respect Pat's remark about leaving some quality in here, to talk more about that.

DR. CHILDRESS: I think that is fine. We will take this more as a comment rather than a question. I will take two more, three more very quick ones because these issues will come up substantively with the people we are going to be talking to later today and I want to keep on some rough schedule. I have Arturo, Diane and then Trish for very brief comments.

DR. BRITO: Given what we heard this morning,

earlier from Bill Freeman and his crew, you talked about how there is no regulations governing research involving adults diagnosed with that condition, diagnosed with mental impairment, what are your recommendations, I know at the end you talked about policies, et cetera. But what, let's say we come up with a policy, what is to say that is going to be any better implemented for this group than what we have heard this morning that it really hasn't been a burden to the limitation of the common rule for anyone. What would you recommend? Is this something that we are going to decide to do? Recommend legislative action or how far do you take it?

DR. CHILDRESS: I am just not sure that your comment, after it captures what the team this morning presented, that there is no implementation.

DR. BRITO: No, there is no, I shouldn't say that. What I am saying is, in your paper, it is very comprehensive, et cetera, but are you recommending, are you going to recommend that we come up with a policy for the mentally impaired or legislative action or what?

DR. DRESSER: I don't think I have the power to make that judgment. I think that is your decision. I think a lot of people feel it is needed. They think it is needed and there are a lot of articles out there calling for it. Another part of your point, though, I think,

relates to Zeke's remark, how can we get these implemented. I think there are lots of people out there on IRBs who act in good faith and would make a valiant effort to apply any regulations that came out. On the other hand, I think you always have to remember that these have to be implemented by people who are not experts, people who are just reading what you are giving them in the regulations and then maybe a little background.

So dealing with complexities of, say, the difference between people with a psychiatric problem versus dementia, you know, all the diversity of this population I think on the one hand that would be great to be very nuanced but on the other hand if you want to get these implemented I think you have to think simple, simple, simple, as simple as possible or as reasonably possible.

DR. SCOTT-JONES: My comment has to do with our consideration of children and adolescents. You made several nice references in your paper to the parallels in research with children and research with persons who are called decisionally impaired or incapable or whatever term. I think that because children are included and are implicated in a lot of the discussion, we should be really careful about the term because their thinking is qualitatively different from adults but it is not properly called decisionally incapable or impaired because the way

they think is developmentally normal so I think attention to the language and categorization of various populations would behoove you and be important.

DR. CHILDRESS: Last comment.

PROF. BACKLAR: I have actually two comments. One is I really want to second the comment you made, Rebecca, about the population generally and the issues, not this population alone that we were just talking about, the problems with the capacity, the consent. As you found out in the radiation committee studies so that whatever we do here, I think will be very applicable to a much broader group and that it is interesting to focus on this but think about the ramifications of how this may improve generally the issues of consent.

The other was a piece in your paper which you mention about imaging and I am a little concerned that we, you have on page 13, you talk about imaging studies and I noticed that in all of our discussion in much of the literature, everybody is concentrating on drug wash-outs and really never talks about what goes on in imaging and the drug wash-outs there and the pain that is suffered. I am hoping, not necessarily as to talk about this more today but this is something I think that we should explore and examine and maybe we can talk about it later at another meeting.

DR. DRESSER: Just to comment on your first point, I think if the committee were or the commission were to come up with an ideal definition of capacity to make research decisions, that would have broad implications and be helpful for all sorts of other kinds of research.

DR. CHILDRESS: Rebecca, we thank you very much for joining us today and for this. I don't know that you heard any specific suggestions for revision but if you would like to make any changes, and submit again, we would be delighted to have this paper as part of our work and look forward to incorporating it into the report. Thank you very much.

DR. DRESSER: You are welcome.

PROF. BACKLAR: I think it is wonderful.

DR. CHILDRESS: We are very glad to have with us now Dr. Rex Cowdry who is acting deputy director of the National Institute of Mental Health. Prior to this position, when he was the clinical director of NIMH and the chairman of the medical board, the National Institutes of Health, clinical center and chief executive officer of National Institutes of Mental Health. Thank you very much for joining us today.

We have asked, he will join us today to speak for about 10 minutes and then to allow time for questions and discussion. I have asked Dr. Cowdry to indicate first of

all whether there is a need for special guidelines and protections in this area and apart from the question of need, if they are proposed, what kinds of directions they might take and what kinds of ethical issues. Thank you very much for joining us.

**Agenda Item: Continuation of Discussion - Dr. Rex Cowdry, Deputy Director, National Institute of Mental Health**

DR. COWDRY: It is my pleasure to receive an agenda that includes a dress code with it and to be invited to a gathering of a formal commission which has an informal dress requirement. I was up until 2:00 a.m. trying to figure out how to condense what could be a very lengthy discussion into a 10 minute presentation and I have not found the answer to that so I hope you will bear with me a bit as I go through this.

I want to make a number of observations. First of all, I come to you, I will make the usual disclaimer that what I am saying has not been reviewed up the department, et cetera, and represents my own perspective but I should tell you something about my perspective. I come to you as someone who has done clinical research in bipolar and borderline personality disorder, as someone who has served as acting director of the National Institute of Mental Health which has obvious implications for the topic

of today and as someone who has experienced first hand mental disorder both in my family and myself in terms of a major depression so I come to you with both a variety of bases for at least holding some opinion.

I would like to make several observations. First of all, I don't think researchers have done a very good job of educating the public about medical research, and about the understanding that outstanding medical treatment requires research results. Understanding the treatments of research depends on having citizens who volunteer to participate in controlled clinical trials, and understanding that discovering the cause of illness and mental illness usually requires citizens who participate without immediate benefit to themselves.

Another observation is that research in some ways has actually been less controversial than treatment in the mental illness area. By whatever measure, there are proportionately far fewer complaints about research participation than clinical care. That may relate to the selection of research participants, the education of research participants in the course of research, better staffing because of the needs of the research and the research setting, closer clinical observation that is inherent in good research.

This does not mean that there are no problems.

In fact, there are substantial ethical issues as you have recognized that reach, in fact, well beyond issues of informed consent. I thought the most useful thing I might do is present a series of concerns that I have although I must say I have been very reassured by what I have heard firsthand today and secondhand about the deliberations of the commission.

I am very concerned that we avoid polarization and demonization in this process. I encountered statements which suggest that researchers are primarily motivated by financial interests or career advancement. The primary purpose of placebo studies is to induce suffering, that research participants are, quote, martyrs in the cause of science, that researchers are themselves not concerned with the best interests of the research participants and that the history of psychiatric research is replete with egregious examples of misconduct.

I believe each of these statements is factually false. We must understand the vast majority of research and researchers inflames rather than illuminates the very real ethical issues facing them. On the other hand, occasionally researchers themselves will assert the critics of research don't care about progress on disorders, don't understand mental illnesses, value abstract principles over the relief of human suffering and are themselves motivated

by either a narrow ideology or by their own career advancement.

Now, such assertions also torpedo meaningful discourse and stand in the way of researchers themselves coming to terms with the ethical complexities of our chosen field.

I am concerned that the process recognize the vital importance of research in developing the understanding of the causes of these illnesses in developing the crude treatment. So I won't say anything more about that. I think that is self-evident.

I am concerned that we do not know and therefore we cannot specify in regulations the best protections. What methods of assessing competence are most effective? What is the appropriate balance between full disclosure and having a comprehensible, written informed consent form. How can continuing oral communication and consent be conducted in the course of research and documented? What alternative means of presenting information and obtaining consent are most effective? In which situations such as a video tape, presentation by a research educator, presence of a family member, use of a test of comprehension?

What are the benefits and disadvantages of appointing independent patient advocates who are using consent monitors? What methods of presenting randomized

double blind treatment studies are actually most successful at combating what has been termed the therapeutic misconception, the idea that research is primarily intended to involve someone in the individualized and best treatment for them.

We can, however, I believe, develop ways of encouraging or indeed requiring attention to these issues, both by the investigator in the process of developing a research protocol, by the IRB in its review process and by funding agencies in the process of deciding whether to fund specific clinical research. I am concerned that individuals with mental illness not be further stigmatized in the effort to provide appropriate protections. Individuals with mental illness are not a uniform class of individuals with diminished capacity needing uniform protections. I think I am an example of that fact.

Even a specific diagnosis, with the exception of disorders such as advanced Alzheimer's Disease, for example, does not correlate closely with capacity to consent. Although some diagnoses such as chronic schizophrenia may signal the need for careful attention to assessing the individual research participant's capacity to provide such consent and the need for such protections which might include specific assessments of decisional capacity, specific tests of comprehension or the

participation of additional individuals such as family members in the consent process.

Protection should be based on specific characteristics of the research such as the benefits and the risks, on specific characteristics of the potential participants and on specific characteristics of the potential participants and on specific characteristics of the research setting. That makes the task of developing a set of specific regulations to cover all circumstances different and that, of course, is one of the reasons that the IRB situation, the IRB mechanism was developed in the first place, to provide flexibility within the context of a structure.

I am concerned that proposed regulations dealing with the institutionalized mentally disabled will be dusted off and used as a starting point for considering new regulations. I have seen a number of discussions in which objections to these regulations were dismissed as merely researchers resisting change. I believe these regulations were and are fundamentally flawed and that conceptualization and permanent unjustifiable stigmatization of those with mental illnesses. All individuals with mental illnesses are treated as a class, subject to coercion and protections were applied to all individuals within its ambit.

It links individuals with mental illnesses, which is, in fact, a heterogeneous group with regard to capacity with prisoners, all of whom are under control of the state with children, all of whom are legally incapable of consent and with fetuses, all of whom are, needless to say, unable to consent themselves to research.

This is the wrong class to identify. It should consist of all individuals with impaired decisional capacity. Having said that, there is a class of individuals with analogous issues common to the entire class, namely individuals who have been involuntarily hospitalized and are thus under the formal control of the state. I think, in fact, that is an extraordinarily small, vanishingly small proportion of individuals participating in research. My view is that that research ought to deal specifically if it occurs with issues that are unique to involuntary hospitalization. They are the only group on which one can connect such research but other aspects of mental illness research can be generally conducted quite satisfactorily on the individuals in other situations.

I am concerned that issues of mental illness research and individuals with mental illness will be characterized as fundamentally different than the ethical issues in other populations when existing research and theories suggest the opposite, as you will hear.

The adequacy of informed consent is an issue across populations. Some proportion of so-called normal individuals, and a larger proportion of individuals with acute or chronic medical conditions not seen as affecting competence to consent or decisional capacity in fact show significant problems understanding complex consent forms, confused research with treatment, have complex motivations including altruism for participating in research.

The problems are more pronounced in some mental illnesses but are not fundamentally different in principle. In addition a number of illnesses not classified as mental illnesses all have almost by definition similar problems with decisional capacity, transient and progressive organic dimensions, certain infections of the brain, certain endocrine and metabolic disorders.

I am concerned that policy not be based, as was alluded to earlier, on bad cases. As a primary example, because it has been so prominent over the last four or five years, let me take the UCLA case. First, there is no question that the written consent forms used in the study did not provide the disclosure required by regulation and by good practice. The OPRR report performed a valuable service by specifying in greater detail the elements of informed consent which must be in the written consent form and how the consent form must deal with issues such as

communication of risk, the differences between treatment, clinical treatment and research and the additional information which must be considered and communicated during informed consent as the research progresses.

However, you and I have been exposed to only one side of the UCLA case. The information which the plaintiff in a lawsuit has conveyed in what must be described as a legal and public relations campaign during which they have made numerous allegations about the research and clinical care provided while refusing to allow UCLA to present their perspective on the case by invoking confidentiality privileges.

We will never know how adequate the continuing oral consent process in fact was or the adequacy of the clinical care or the truth of numerous allegations because the plaintiffs, after trying the case extensively in the press, refused to go to trial leading to dismissal of the case. You will never hear from other participants in the UCLA research because, having sought out and interviewed other participants, a major TV investigative program apparently found that what these other participants in the UCLA research had to say about the research was not sufficiently newsworthy or provocative to present along with the allegations.

Now, I will not defend aspects of the UCLA

situation. We totally accept conclusions of the OPRR report in its entirety and have taken very active steps to disseminate to all our grantees conducting clinical research. I only know that other aspects of the case can't be relied on in developing public policy. I would say the same thing about the New York state case. Found in the New York state case is sort of a misnomer because there has never been a hearing about the actual facts of research in New York state. None of the plaintiffs in the case have ever been involved in a research project in New York state.

In this regard, the New York state decision arose out of a unique situation in which there was no authority for the Division of Mental Hygiene to issue the regulations, but without any evidentiary hearing have been broadened to reach possible conclusions which I must say I think the commission needs to be concerned about because the possible conclusions reached by the court, the tentative conclusion would have devastating consequences for pediatric research in general, not pediatric research in mental illness but all pediatric research because one of the tentative conclusions reached by the court was that it may not be possible for parents to consent to their child's participation in research which will not be of immediate and direct benefit to the child.

Let me tell you that if that becomes the law of

the land, we have seriously undermined the capacity to do something for our citizens who have autism, possibly for attention deficit disorder who have mental retardation, developmental disabilities or diabetes, for that matter. It establishes a principle that I think needs to be examined in detail.

So that is sort of an elaboration on the idea that single bad cases don't make good policy. I am concerned that some individuals have expressed the belief that we as an institute have neglected issues related to the ethical conduct of research. These issues have been a deep concern of many of us in the institute over the 20 years I have been in government service at the NIMH. We are proud that a disproportionate amount of research, including research that you will hear about subsequently, in fact, from Dr. Appelbaum, has been funded by the NIMH. For over 10 years the intramural program has been extensively involved in the NIH clinical center in developing the conceptual underpinnings and practice of the durable power of attorney in research settings, grappling with how substituted or proxy consent can be ethically implemented for research.

For over five years, NIMH and OPRR have co-sponsored training for IRB members in issues related to research with the mentally ill. Recognizing the need for a

single source book for our investigators, we have financed the development of a guide for investigators which is now in its final draft. Given the clear need for additional research, three years ago the NIMH issued the first program announcement on informed consent research, an initiative which has now broadened to the majority of NIMH institutes who are co-sponsoring an RFA on informed consent which attracted 95 applications and is currently under review.

We sponsored a conference three years ago dealing specifically with ethical issues in research involving children which was published as a book last year. It addresses a broad series of questions including issues of parental consent, child assent. What in the world is meant by the term minor increase over minimal risk? Without reaching a conclusion, I must tell you. And new data about children's perceptions of their research participation, some of which surprised even me. For example, I would not have guessed beforehand that children who have both been sent to the principal and have had a lumbar puncture in the course of research on their disorder would find going to the principal a more traumatic experience.

The NIMH has conducted a series of interactions with investigators and the FDA around the ethical issues of pharmaceutical trials, particularly the use of placebos and that, I think, is one of the predominant ethical issues

that goes beyond informed consent that the institute and society is going to have to grapple with over the next several years.

We began a uniform process the last year of reviewing consent forms prior to award or re-award of a grant within the institute, again serving as an additional level of review or protection and, indeed, that has led to some negotiations and changes in consent forms already.

Six institutes of the NIH with NIMH serving as a leader developing a conference focusing on how IRBs can best address their responsibilities with regard to potentially vulnerable populations, specifically cognitively impaired subjects. We expect this conference to be conducted in the form of sort of a consensus conference with presentations to a panel, discussions by the panel and a report from the panel dealing with additional protections which the IRB should consider, as well as broad policy issues such as proxy consent and the durable power of attorney.

Dr. Childress, what is your desire? I could talk for another three minutes about the major issues we face or we could open it for discussion. It depends on your time management purposes.

DR. CHILDRESS: We are running a little behind but that is to be expected. Three minutes?

DR. COWDRY: Yes. Let me talk about it.

DR. CHILDRESS: And then we will open the floor for discussion.

DR. COWDRY: Study design is crucial, particularly the issue of non-therapeutic research, research of no immediate direct benefit to the participant. Is it inherently irrational to participate in such research as some asserted? Certainly the therapeutic misconception, the notion that participants still believe that they are receiving direct benefit from such research is problematic. That is going to try our abilities to find ways to be sure that individuals understand the research. I don't think we know that. We can't put it into regulation but I think we can develop research and part of that is going to require diversity. IRBs are going to have to, and investigators are going to have to explore different approaches to see, frankly, what works.

Study design issues. Our challenge studies which evoke symptoms of panic disorder or psychosis or in case of minor research, borderline personality disorder, ethical. Challenges may give invaluable insights into the biological causes of symptoms. Strangely transient clinical worsening is not only a risk but in a sense actually a goal of the research as part and parcel of the research design but it poses an ethical issue that we cannot ignore.

How about placebo arms? Is it ethical to withdraw a participant from active medication which appears to have been beneficial? Individuals who do not relapse in such a situation have gained valuable information and less exposure to significant medication complications. Individuals who do relapse may not rapidly recover. To some extent, this controlled discontinuation mimics the natural course of these disorders because most patients with these disorders at some point discontinue medications on their own without the kind of supervision that occurs in research so it is really not, what I mean to suggest is that the issues are complex. There are not any simple answers to the question of whether placebo periods are ethically defensible. There are complex arguments on both sides.

The issues with regard to therapeutic trials of medications and placebo arms are even more complex because we deal also with the regulatory agency, the FDA. Generally, as a principle, although they will insist that placebo arms are not required by regulation, placebo arms are, in practice, necessary to convince the FDA that the drugs are affected. This poses a very interesting and troubling dilemma and I think makes it incumbent on us to further explore what we have begun to explore which is what are the alternatives to placebo designs that are

scientifically acceptable to the FDA and ethically more acceptable to us.

The role of the clinician investigator. Interesting issue. I believe it is vital that the moral tension between optimal care of the patient and involvement in research be internal to the investigator. The well-being of the patient must always be a primary concern of the researcher. On the other hand, separating the roles may assure that the patient's interests are well represented. There is a potential cost or moral tension inherent in that because it is externalized.

A related issue of role conflict is who assesses competence and I think that is an issue that sounds like will be addressed in the course of the discussion. IRBs, what should IRBs, what could IRBs, assuming we believe in the IRB system as fundamentally like a democracy, namely it will not be perfect but it is the best system developed to date. How can we help the IRBs tailor their protections to the setting, the specific patients and the benefits and risks of the research? The IRB has the authority to require a wide range of potential protection. How can we encourage the exploration of the usefulness of these protections?

Finally, the issue of substituted or surrogate consent as I referred to earlier, I think is a critical

issue. I think that it is one that this commission cannot avoid. The questions of how to deal with research with individuals who have some impairment in their consent is crucial. I think it is crucial that these individuals continue to be involved in exercising whatever capacity they do have for asset. But the question of who can represent these individuals at this, how can it be done in a way that is both ethical and not, how should I describe it, fatal to the research process I think is critical.

I think that the issues with regard to pediatric consent have to be grappled with. They are substantial. But I fear the result if these broad issues of why we need research with these populations that we have put these disorders is not taken into account. Durable power of attorney I think is an important issue to address because I think it offers some potential solutions to some of these difficulties. It also points out that all competencies are not created equal. That is it may be a flexible mechanism in that I may be able to recognize who can represent my best interest even if I cannot fully appreciate the complexities of research that I am being asked to participate in.

But I think it is an interesting mechanism. It poses fascinating ethical dilemmas and it also is one that we would welcome attention to from our perspective.

DR. CHILDRESS: Thank you very much for sharing this with us today. We will plan to take our break in about 10 minutes. I know there are others who have questions but let me just, since we are hoping to issue a report and make some recommendations late in the fall, you and I have talked in passing about when the consensus conference might occur and obviously that is something we would like to relate to, both being there but also being able to draw the results for our own report. Do you have any sense of the time yet?

DR. COWDRY: One event, that may cause us to reconsider our timing. We were actually thinking of the November-December time period but it may be that we have to explore efforts to move that forward in time if you are operating on that --

DR. CHILDRESS: That is our goal but we can talk.

DR. COWDRY: I will take that back on Thursday to the group.

DR. CHILDRESS: Okay, and then we can talk further about it. Trish is on with a question.

PROF. BACKLAR: It is actually more of a statement than a question. I think as we continue today to talk about these issues that it is extremely important to make a distinction between not only the consent process but how the research goes on after and how somebody is

protected who made news or had no ability for decision making during the process of the research so there are two parts to this.

DR. COWDRY: It is one issue that I think in some sense the durable power of attorney provides a strategy for dealing with because prior to, presumably prior to impairment of decision making, it enables appointing someone who the participant believes will represent their best interest but I know there are issues for that mechanism also.

DR. SCOTT-JONES: I have two questions. First, I was really glad to hear you say that we should avoid polarization between researchers on the one hand and communities of participants on the other hand and I think the avoidance of polarization should be on both sides, from those who are concerned about research participation but also on the part of researchers who may think that anyone who doesn't participate in their study is apathetic or antagonistic to research.

It seems that the responsibility for forging good relationships rests with researchers who want to conduct studies so I was wondering first what you think can be done to improve the relationships between researchers and communities of participants. What can researchers or institutions do to have outreach, to have educational

efforts?

Then I have a second question. You talked about how the consent process overall isn't all that great, and there are many of us who have that concern. In fact, in the Dresser paper we just read, there is a reference to a study that showed that parents consenting for their children often really did not understand much about the research and so their informed consent isn't genuinely informed.

So it seems to me that your comments about that would make us not less concerned about consenting on the part of persons with psychiatric disorders or mental disabilities but more concerned about the consent process overall and insuring that persons can give genuinely informed consent.

So my second question is, what can we do to improve the consent process overall?

DR. COWDRY: I think those are two excellent points. Let me address the second one first I think. The adequacy of the consent process varies, there is no question about that. I happen to believe, and I usually start out any talk that I am giving with the notion that research has to be a collaboration. There is really no alternative to it being a collaboration between the researcher and the participant in the research.

Interestingly, I have seen actually less polarization between researchers and participants in research than I have seen between the research community and people who are not participants in research, that is, who bring other perspectives to bear on it, the protection of advocacy perspective, for example, that is taken by the attorneys for the plaintiffs in New York state. I think that is where the most problematic polarization occurs.

For example, I find the National Alliance for the Mentally Ill's perspective on research deeply consistent with our own perspective as an institute. I believe that a number of their specific recommendations about having medications available after completion on a compassionate basis, for example, are important.

One thing that addresses the other point you made about outreach is the recommendation that there ought to be members of the IRB considering I think actually it ought to relate to a wide range of research, not just cognitively impaired, potentially cognitively impaired subjects. There ought to be individuals who are familiar with the disorder.

Now, that may mean that IRBs that handle a huge, wide range of, and a large number of protocols may have to find another way of doing their business or that individuals may join the IRB for discussion of particular types of research protocols but I find the participation of

either someone who themselves has the disorder or has a family member with the disorder or in a sense who represents and knows the disorder and its difficulties firsthand invaluable.

Some of our research centers have actually started community outreach literally. I mean, clearly that goes on with National Alliance for the Mentally Ill and the National Mental Health Association. But I think more broadly that is necessary, particularly in some of the very controversial areas. We have a number of studies of attention deficit-hyperactivity disorder in children. That is potentially a very contentious issue in the community. It was utterly important that those projects from the start be designed so they were just studies, that they did not disproportionately involve minority communities, for example, in the study, but that they did involve minority individuals.

That there be active discussion with the community and in a way that is partially in the self-interest of the research, quite frankly. It is what you have to do to be able to conduct reasonable research.

Do we need to encourage that? Absolutely. Can we do it by fiat? I hope we can do it by persuasion and self-interest because I think that is what leads to both good research and frankly as we know from doctor-patient

relationships, the relationship between the doctor and the patient is the most powerful predictor of whether a malpractice action will be brought.

DR. CHILDRESS: Thank you. I have three people on the list and we will take our break. Dr. Cowdry has indicated he will be around most of the morning so there may be some things you want to raise with him over the break and I appreciate your being with us for the morning. I do want to note that we will hear in September, the plan is to hear in September form a wide range of patient and family groups and organizations so we do intend to conduct a public hearing at that time. We will announce and hope to have as broad a range as possible for that.

I have Rhetaugh, Alex and David and then we will take our break.

DR. DUMAS: I appreciate your perspective and I am pleased to have us move to the idea of decisional impairment and I would suggest rather that we might think of refining that even more so that it would not stigmatize any particular group. The whole idea that subjects have questionable decision capacity because the determination of decisional capacity is as complex as all of the measures that we are using so I like having the category broadened.

I am also very much aware of the complexity of this whole business of informed consent and you mentioned

something about test of comprehension. I think that is very important because I think that we have been willing to assume that people are informed if we give them adequate information that we feel is adequate to inform them but how they understand it, how they process it, what it means to them is yet to be determined. So I think we need to spend a little bit more time on measures of the state of being informed.

The other thing is that, and I think that would take into consideration this whole business of maybe questionable decisional capacity rather than impairment would take into consideration children whose decisional capacity is not impaired for their developmental phase but may be inadequate for the purposes of the research. I also am very interested in the Los Angeles case and I am disturbed by it. I think there is a lot to be learned from it and I think that what can be learned can indeed form public policy so I wouldn't dismiss summarily the opportunity for using that case to inform public policy.

DR. COWDRY: I really don't have any comment. I agree completely with that, and I think the broadening actually helps address, I mean, my reaction to the study that finds that parents can't report the content of the informed consent material they have been given is that this signifies that the issue is a broad one. It is not

confined to specific diagnoses or categories. It is a broad issue of how people are involved in that process.

On the other hand, it also indicates that informed consent is never going to be able to be the sole bulwark of protection. It is, I think, naive to put all our eggs in that basket. I think the whole processes of training ethical investigators having IRBs that pay attention to these issues in the review process, having funding agencies that tend to these are integral and invaluable and an informed consent, while vital and important and while presenting an ideal by itself isn't going to do the job.

DR. CHILDRESS: Alex, briefly, and David briefly.

PROF. CAPRON: I think I may follow up with a letter because you raised so many things and we don't have a lot of time. I want to just inject here clarifications from your, a couple points from your very interesting testimony. You -- would you provide us with a copy of your testimony?

DR. COWDRY: Sure.

PROF. CAPRON: Well, we will have the transcript. You noted that the New York decision in the TD case, you thought threatened all pediatric research. Isn't the opinion limited to children who were institutionalized?

DR. COWDRY: The problem is that the

constitutional principle that they relied on is applicable to all the children. It is a matter of status as a child, that parents could not as a matter of constitutional law, the court was concerned, I don't think they actually reached this decision but they expressed a tentative opinion that no parent could consent to a research of greater than minimal risk which is a great variety of research that doesn't offer the principle of direct and immediate benefit to that particular child.

So that is what I meant by that principle clearly applies to all the research involving children. In the course of that, I must say a number of statements have also been made in the course of the documents that I think need to be checked out because some of them by my read of them are patently wrong about what federal protections actually are in some of these areas.

PROF. CAPRON: I hope we will get further clarification on that. You mentioned something with which I would certainly agree that the involuntarily institutionalized should only be used in studies about institutionalization in effect, about human conditions that are relevant because those would be the only studies that could not be conducted on those not so institutionalized. I wasn't clear if you were drawing a difference between those who were voluntarily institutionalized and those that

were involuntarily institutionalized.

DR. COWDRY: Yes, I was, because I think their legal status is fundamentally different. I think the voluntarily institutionalized present a range of issue but it is not, the principle isn't as clear-cut.

PROF. CAPRON: But don't we know from many years of examination of that field that a great many people who are voluntarily institutionalized are in effect volunteered into it under the statement if you don't go in voluntarily where you will allegedly maintain greater ability to control the situation, we will involuntarily institutionalize you?

DR. COWDRY: I hope that is not the exact form it takes but there certainly is an issue in that regard.

PROF. CAPRON: So wouldn't a more conservative approach encompass those who are institutionalized as those who are in a particular status unless the illnesses from which they suffer only occur among the institutionalized it would be more respectful of the principle that you seem to be articulating to conduct the research on their illnesses on those people who are not under that additional constraint.

DR. COWDRY: I would make the same argument that I generally which is that this is a heterogeneous group. People are voluntarily hospitalized. People who have

participated in my research studies at the clinical center were voluntarily hospitalized but they are fundamentally no different than an outpatient participant in research. On the other hand, there are people who are acutely hospitalized from the emergency room in whom there are issues about the voluntariness of their admission. I think those get attenuated when it comes to them actually facing the decision about research participation and I think actually it is much more of an issue for the clinical decisions than it is for participation in particular research programs.

So I am just concerned again as I was with the original regulations that it casts such a broad net that there are significant adverse consequences as well but I agree with your point that there are individuals in whom have to have a heightened concern.

PROF. CAPRON: I guess my final question is you provided early in your talk a very useful list of things we don't know about the best way to conduct research and to get consent from those with mental illness. In effect, you returned to some of that list in your major issues at the end.

I thought it was a very helpful catalog. They are not unfamiliar issues. They have been around for 20 years and I guess my question would be, could you provide

us with a listing of the results of research studies that the National Institute of Mental Health has sponsored over the last 20 years which answer those questions or at least address them?

DR. COWDRY: Sure, that would be helpful, thank you.

PROF. CAPRON: I hope when we get the list you will come back so we can discuss it.

DR. COWDRY: Be happy to do that as well.

DR. COX: And hopefully very quickly. It deals with the issue of consent and it deals with the observation that you made that a large number of patients, not just in the area of mental health but I would extend it even further, have this misperception that they are, in fact, getting treated when in fact they are undergoing research so that is very puzzling to me on its face value but when I reflect on it, it strikes me that the most likely reason for it is because the people who have personal self-interest of doing the research are the ones doing the consenting.

I wonder then because you also made the important statement that informed consent by itself wasn't going to be the way to go, first of all, do you think that personal self-interest of the researchers has anything to do with the fact that the subjects misperceive what is going on and

second, do you think having somebody else do the consenting besides the researchers may be a way to resolve that problem?

DR. COWDRY: I hate to put it this way but I think in some sense it is an empirical question. I think in some ways it is a mistake to not have the researchers fundamentally responsible for the consent process. The question is not just in this area but how you in general oversee the process to be sure that you are getting reasonable results out the far end. I didn't mean to imply that informed consent wasn't vital in any sense. It is utterly a bedrock but it is not sufficient in itself. Just like reviewing the written consent forms is never going to be sufficient because the only way in my opinion that I get adequate consent is by yes, having a six page single space consent document but then by having three hours of discussion about what the research involves that is not, you will not find written down anywhere.

So I think it is a complex issue. I don't think that there is a simple solution like having someone sit in on the moment of signing of a paper that is going to solve that but I think there are a number of experiments underway about approaches, having someone who has been through the research, for example, serve as an educator of potential participants and this is one of the things that we hope our

book for investigators will have some ideas for IRBs to explore different ways that they can be assured that participants are providing better quality of consent.

DR. COX: Just a follow-up. It doesn't sound like you believe the conflict of interest inherent in the researchers doing the consenting is a significant enough magnitude to be of primary concern.

DR. COWDRY: I think it is possible that some of the research misconception arises from that. I think the majority of it arises from very human needs and desires on the part of research participants to find something to help their illness. I must tell you that is a pure assertion, that is not --

DR. CHILDRESS: We are going to have to break because, pretty quickly. Harold wants a final word and then we are going to break.

DR. SHAPIRO: Two comments. One, the original draft of this meeting thing has a specific and controversial issue regarding whether a researcher can enroll his own subjects. I don't know what the final draft shows but it will be interesting.

DR. FREEMAN: I can get that for you.

DR. SHAPIRO: I just wanted to understand Alex's question. I wasn't quite sure the kind of cases you were asking for information about. You were asked to report on

some studies, cases.

PROF. CAPRON: There was a long catalogue of researchable topics. We don't know about it. I mean, they were phrased in the same way that some of them would say we don't know what basal cell carcinoma does under this here. I assume that if the director of the National Cancer Center were here and listed off a lot of interesting topics that have been around for 20 years, there would be a catalogue of research studies that have been addressing those topics. I want to know whether we have a similar catalogue of funded research by the National Institutes of Mental Health on these topics over the last 20 years.

DR. CHILDRESS: And we will be hearing about one of those later this morning so that will be just one example. Well, thank you very much for joining us. Really appreciate this. I know there are other questions. Some of these will come out in the discussion later this morning but you can also get Dr. Cowdry. We will start again eight minutes, 20 after.

(Brief recess.)

DR. CHILDRESS: Okay, we are ready to get started. I have also been asked to ask everyone, including myself, to use the microphone when we speak. Harold has been doing a great job doing that. Some of the others have not done so well and people in the back are having trouble

hearing us especially since most of us are looking the other way so be sure to use the microphone.

DR. SHAPIRO: Someone has pointed out that there is a pair of glasses, rimless glasses left in telephone booth number two. If anyone can't see and wondering why --

DR. CHILDRESS: Thank you. For the next period we are going to continue discussion of decision impaired subjects and hear two different perspectives on research with such subjects and what guidelines if any might be appropriate, what special guidelines if any might be appropriate. First, we will hear from Dr. Nina Schooler who is director of the Psychosis Research Program and professor of psychiatry and psychology at Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center. You have in your packet one of her co-authored articles. This was circulated to you in advance of this meeting and ask her to speak for about 10 minutes and then we will have time for discussion and we will turn, after she is finished with her discussion, to Dr. Shamoo.

**Agenda Item: Continuation of Discussion -- Drs. Nina Schooler and Adil Shamoo**

DR. SCHOOLER: I think I have been invited here today as a case example. I am a researcher. I have been conducting research with schizophrenia patients, subjects, for almost 30 years. I started when I was at the National

Institute of Mental Health and in that environment I had responsibility for design of projects, analysis and interpretation of results but I didn't have direct contact with the patients who agreed to participate in the research and also didn't have direct experience with the design of consent documents and submission of protocols to IRBs. Now, some of the work that I did actually took place before there were such things as IRBs so that there is, but that is another story, but for the past 10 years I have been at the University of Pittsburgh and conducting research with patients who suffer from schizophrenia.

In that context, I have been forced, required, chosen to develop my skill as an ethicist but I would say that that is not my profession and I have had a couple of opportunities to work in issues that are relevant to this. For example, I served as a member of the Committee for the Protection of Human Participants in Research of the American Psychological Association and I served on a panel most recently to revise the ethical guidelines for another organization that I belong to, the American College of Neuropsychopharmacology.

But my perspective in this has been as someone who is interested in a series of research questions that require me to obtain consent from patients who will be participants in the work and who will join with me in this

collaboration and what I would like to do is to share with you over the next few minutes some of the things that I have learned over the last few years and some of the practices that we have in place that make it plausible for us to do the work that we do.

First of all, we operate under both with research grants that come both from the National Institute of Mental Health so therefore they are federally funded and also research grants that come to us from various pharmaceutical companies because one of the questions that I am particularly interested in and where much of my expertise has been developed is in the area of effectiveness, efficacy and effectiveness on psychotropic medication for schizophrenia.

One of the things that I think has become very clear to me in the course of conducting the research that insuring that people understand what we are going to be doing is enormously, enormously time consuming for us and for them. It turns out that the informed consent documents that we design which meet the regulatory requirements and our institution is very careful, are documents which are difficult for us and are difficult for the patients who we enroll in our studies to understand and as a result we find that internally to our own group, we developed a series of secondary, I think of them first as both hurdles to getting

into the research projects and secondly maintaining information about the research projects that patients are involved in.

Let me describe one such study in particular. This is an NIMH funded study which is comparing two medications, two new medications for the treatment of schizophrenia in patient who were called treatment refractory and what that means is sort of shorthand, I guess like decisionally impaired. It is shorthand for not having responded well to other anti-psychotic medication.

We have a whole series of criteria whereby we know that patients meet these criteria. These are discussed with clinicians and a decision is made on our part that this person is probably going to be appropriate for participation in this setting. This is a study that was conducted both with inpatients and outpatients.

If the patients are inpatients, the first thing that happens is they tour our research ward. The research ward is called the Special Studies Center and it resides at a state hospital in the State of Pennsylvania. If they are interested, given a very rough notion of what this will involve, namely we are going to be comparing two medicines, would you be interested in participating. In order to participate, you have to live on this research ward. They take a tour. That is the first step.

The second step --

DR. CHILDRESS: Are they already in the institution?

DR. SCHOOLER: That is correct. These people are in the institution. They are not hospitalized for the purpose of the study. They take a tour and they see what the facility looks like. Now, I will tell you quite candidly that our ward is one of the nicest wards in the hospital. It has, I do believe, better staffing than other wards because in addition to the legally mandated staffing which is what the state provides, we have research personnel there as well, and in addition the state hospital personnel who work there have been educated over the years and we have the opportunity to provide certain kinds of things in that ward that are just not available in the rest of the hospital, having to do not so much with the physical plant because our physical plant is not particularly attractive. We are not one of the newer buildings at the institution by a long shot.

After that, and before all of this, then what happens is we will make a contact with family members if there are family members available for this patient, and secondly if the patient agrees to allow us to contact their family member. I will say again that in many instances where we know that there is a family available but the

patient is hostile toward our contacting the family member, we are relatively reluctant to enroll this patient in the research project. Now, we may be discriminating against the patient in this way but we are concerned that if there is a family and the patient is in a hostile relationship to them, that there may be difficulties in the future.

At this point, the research project is explained to the patient by both the person who is our primary recruiter and also by the physician who will be involved with the patient and the patient's care so there will be probably a one-hour discussion with each one of them. If at this point everything seems a go, patient will be transferred over to the research ward because it is our general belief that we don't want to conduct the, quote, formal consent process before the patient has adjusted to the living environment because the work will be conducted in this residential setting.

At that point we proceed with the consent document. The consent document for this particular study is about seven pages long. It is single spaced and it has a lot of information in it. We have some concerns that patients have trouble in assimilating all this information so what we have developed is a brief questionnaire which is here which essentially is a true-false questionnaire which embodies for us what we consider some of the critical

points regarding the research.

Now, some of these are true and some are false. For example, one that is a particularly important one to us is the statement that, number five, my doctor which will decide which medicine I am taking in this study. The answer to this one is false. What the doctor will decide is that one or the other of these medicines might be appropriate for the patients who enter the study but not which particular one.

The second one, the question of whether, another important one is that there will be a time that I will not be taking any anti-psychotic medicine. Now, this is a statement that we used in some of our other studies where it is true, studies that do have placebo periods or placebo arms. In this one it is not true but we want to be sure that the patient understands that. We also want to be sure that they understand that they can withdraw from the study.

Now, clearly, these nine items do not represent an informed consent document and clearly these nine items to not adequately and fully summarize everything that is in the seven-page document that the patient has been presented with and has indeed signed. As I said before, I am not a researcher into the informed consent process so that from my perspective, I am not as much interested in the question of well, after we have gone through the informed consent

procedure, how much of it does the person understand? Did they get seven right? Did they get nine right? Did they get three right?

My goal is to be sure that they have all nine right, that in other words they understand what the relationship that we are entering into in the context of this study is.

Now, this study, so that is the, is our procedure. We have a version of this, I have taken out the true-falses so as not to detract from looking at the individual items. A copy of this form which is completed with the patient by one of the research nurses in the project will go into our research chart. It is not part of the hospital chart.

Now, I suppose that there are some who would argue that we are doing this in order to should I say paper the chart and therefore protect ourselves and it may be that there will come a time where a document such as this could serve that purpose but from our perspective what we think we are doing is insuring that the people who are deciding to work with us really understand what they are getting into and that they recognize what are the positive features and what are the negative features.

One of the pieces that has become very, very clear to me as we have been working over the years is that

a primary issue is the one of trust and it goes both ways. We trust our patients that when they say they are going to participate and they are going to do something because most of the people who start this project in the hospital will end up in the community. It is a 29-week study so they will end up in the community. They will not be hospitalized for the entire length of the protocol so that we need them to be sure that they are going to come back and have blood draws every week which are required for one of the two treatment arms of the study, namely clozapine, but since this study is double blind, it has to be done for all patients.

Now, the last point that I want to make is that something that we have learned and that we do and is actually codified in this protocol but not codified in all the protocols that we do but still are practiced is that we believe in what we call wrap-around care which is that if a subject has agreed to participate with us in a treatment trial, that it is our responsibility to provide care after that trial. In this study, the clozapine and resparadone(?) study, we have funding from the drug companies that manufacture each of the two drugs. They provide us with the medication for the double blind study but they have also committed to us to open label medication for a period of time as long as the trial length.

So that we make a commitment to the patients for a period of a year. Six months of that will be the experiment that we need to do and then another six months will be treatment with one or possibly both of these medications and that is something that we were able to negotiate with the drug companies successfully, with difficulty but successfully and is something that I think is very, very important so that we can take the therapeutic misconception, if you will, and turn it into an accurate therapeutic conception for patients.

And, indeed, this is also the case in many therapeutic trials that are designed by the industry. They are what they call open label extensions which make it possible for patients to obtain the medications that one of, the experimental medication that is being studied.

Now, the last point that is wanted to make is that there really are in a sense two questions regarding research and my sense is that we are addressing one of them here which is individual capacity to consent and how to be sure that the individual subject is appropriate for a protocol and does understand what they are entering into. That is what I have tried to address here but the other question which is a broader one I think is the question of whether a particular research study should be done. In other words, should anybody be offered the opportunity to

participate in a particular study or is this a study which is a, for whatever reason, an inappropriate one.

I think that that is another very important issue. Researchers address this all the time so that for instance in deciding whether we will participate in the study, whether we want to do a study, whether we want to design it, we have to feel that it is an important question and I will give you an example of studies that are relatively easy but that we have chosen not to do.

We have, for example, been approached by pharmaceutical companies wanting to know whether we would participate in a study that involved comparing the same drug with a once-a-day dosing or twice-a-day dosing. In other words, we only give it at night or we give half a dose in the morning and half at night. I understand why that is a question that is of interest to the company and it is actually a question of some modest interest because it will protect people at the level of it is easier to only have to remember to take your pills once a day than to have to remember to take your pills twice a day.

My feeling is that it was not an important enough question to engage our group.

DR. CHILDRESS: Thank you very much for the presentation. Again, I remind the commissioners that we will need to be very disciplined in our question because we

don't have a lot of time with each of the three persons and we will have to reserve this afternoon for our discussions but please try to be as disciplined as possible. Trish?

PROF. BACKLAR: Nina, thank you so much. I just have one short question. It is interesting to me that you have this after-care pan, but if it is six months in research and six months after-care, for this population I would be very concerned to know what happens at the end of six months. It is very short. Even a year is short.

DR. SCHOOLER: Absolutely, and thank you for asking. At six months we are not, it is not a here's your hat, it has been nice. At the end of the open period that is what we consider our transition and we are in the process usually of trying to refer the patient to appropriate care. If they come to us from an after-care clinic originally, the deal that we cut with that program is they will come back and we will have usually multiple conferences that involve our treatment to their treatment team that negotiate the transition. We have had some people that have been in treatment with us for periods as long as two and a half years. We try not to do that because we don't have support for that but if we can't make the right referral, we don't refer.

DR. EMANUEL: I took it that this process you do of asking nine questions is really a process not so much of

information transfer but of understanding, assessing their understanding of what they have got. A quick question is, do they have to score all nine or do you just explain ones that they have missed to make sure that they do get it?

The second one is it struck me when you were explaining your consent process, this is minimum five hours and it sounds like very frequently ten hours of consent for a single subject. I mean, there is a cost. One should always remember of such extensive consent which is you can't have a whole lot of subjects in that study and that may significantly impede both from the cost standpoint but also the number of people you can do and therefore the implications you might be able to draw from this research.

And, again, I think in light of the cost-benefit ratio that we are going to have, there is a risk to not doing more patients also.

DR. SCHOOLER: Yes, you are right. Let me answer the second questions first. You are absolutely right. Our subject flow is slow and part of the, but we just don't feel we can do any less than that because the fact is we are asking people to engage over a long period of time and we need them to understand what it is.

Sometimes it is faster, I mean, some people are quicker at it, but it always involves at least three occasions of contact before the deal has been cut and that

doesn't include the contacts with the clinicians who were involved beforehand.

The other issue is it is an issue of understanding for us so we want to be sure that people understand all nine points and that may take a little extra time. It is not a test.

DR. CHILDRESS: I will take four more comments and I have Alex, Eric, Laurie and myself.

DR. CASSELL: This is not directed to you. It is also a comment on Dr. Cowdry's presentation. I think that the thing we have all learned over the years is that all our concentration on the question that is involved in total consent, does the patient understand the consent is very important but it is only part of it. What we really know is that informed consent is a social act and that people, that the impairment in cognition is not restricted to people who are otherwise impaired, that anybody can have trouble making an informed consent, simply if they like the investigator a lot. That is just a fact of it. In the past we have all said that can all happen and then we go back to that form again.

It is my hope that as a result of what we are doing, they will come out of this with some way to make sure that the informed consent procedure is understood as an informed participation procedure. The way a person

becomes a part of something else. I like the nine questions. I think that is nice. My own sense is that is not merely for understanding. That tells a person you are doing that more than just that you want to know if they understand the tripartite way of doing it does a lot more than just see that.

But what isn't clear is exactly what does it do and it is my hope that in the things that will be stimulated by our work in the beginning, what does it mean to participate. That wasn't in the consent. What does it mean to participate? Because you can consent and not participate. All you have to do is not take your medicine, right? And so as I listen I am trying to see is there someplace that is going to tell me that, tell me answers, start answering those questions, even without a research protocol for which you have to have somebody's consent to find out about consent so that is what interests me.

MS. FLYNN: Nice to see you, Nina. I have two issues I would like your comment on. One is I am very interested in the roles of the IRBs in these issues and I wonder if you could share a little bit of information about the IRB that you may be working with at the university, to what extent is there any participation on the IRB of families or consumers, individuals who have personal knowledge of these disorders and might be especially

sensitive to the issues inherent in the cognitively impaired and is there any kind of special training or any kind of particular orientation or is the entire IRB focused exclusively on psychiatric issues? I am interested in how the IRB takes its responsibility and plays it out over the course of some of these research questions.

The other is I wonder if you can comment on an issue that many of us in the advocacy community worry about which is the particular circumstance that many people with schizophrenia find themselves in, in a climate where we have a lot of new and somewhat expensive therapeutic interventions, medications but we are dealing with the population that is largely very impoverished due to a history of discrimination in health care coverage. There is a concern about how much this may even self-represent somewhat coercive potential environment. In other words, if you are a typical person with schizophrenia and you want access to these new treatments, the only way you are likely to get it very well is through a research protocol.

So I wonder if you could comment from your own experience on those two issues.

DR. SCHOOLER: First, let me comment on the IRB. I will say that the IRB is for me an opaque entity to which I send materials and from which I gain statements of approval. Our IRB is a very, has a very large volume and

to my knowledge, it is not particularly restricted to psychiatric. At one time it was divided into two. There was a biomedical and a psychosocial IRB and what they have done is to combine that into one so that there can be meetings every week of some subcommittee or another of the IRB and I think what that means from my perspective what happens is that throwing a hat into the ring, the hat being a research protocol, I have no idea of what kind of a response it will get.

I have on occasion gotten more questions for a study that was going to administer a new medication open label and then two weeks later had a very brief series of questions for a study that did involve a placebo. So it seems to be a very variable process. I know that there are lay members, there are professional members, but I do not believe there to be specific required expertise from consumers or family members regarding psychiatric disorders.

The second issue, having to do with availability of medication, I think that is variable. It varies from place to place. In our environment, virtually any marketed medication is available if a physician chooses to prescribe it. So that means that drugs like clozapine and now resparadone and the Lanzopinen that you well know are available without participating in a research protocol.

Unmarketed medications, of course, are only available through research protocols and I believe that to be correct.

DR. CHILDRESS: I am going to raise the last question and it is a fairly broad one. Having read your very interesting paper, the one you co-authored and we circulated to members, you are very clear there that you think there should not be a radical revision of approaches to including decision impaired subjects in research and your presentation data on current practices, your own current practice and your paper, you seem to suggest that what we need to do is look at current practices and procedures and assess them for adequacy.

Now, I guess there is a couple of parts to this question. One would be do you see the need for any special guidelines for decision impaired subjects, that is, to flesh out what we currently have in the common rule. And are there any particular things that you would feel should not be included, that is, proposals that have been made up for consent monitors or anything else? Just in conclusion if you would give us your reflections along these lines.

DR. SCHOOLER: Let me address the second part first. I was very interested in the comment that clearly engaging in research is, it is a participation but not a consent and that there are all sorts of things about that

that we don't understand. My concern with possibilities such as consent monitors is that they can't be long term participants. In other words, given the issue of cost and so forth, they are not going to be around all the time so that what they are going to, what a consent monitor would have to be or an independent person who is involved with the consent process is going to have to be someone who will have an even briefer snapshot, even briefer opportunity to participate.

And I think that what is more important from my perspective would be increasing education for research. There is no question in my mind that I am better at this now than I was 10 years ago and I have got a better understanding of what is involved and that the people who agree to work with us are having a better shot at it that they had 10 years ago and that is because I have been working at this for that length of time and participating in a variety of things and going to meetings and thinking about it.

The issue for me is I would like to see more people have those opportunities and I am not suggesting, I am not perfect, I don't know that I have got it all right but I am better and I think that is useful. The other question regarding decisionally impaired people and that phrase, I don't think decisionally is going to show up on

my spell check so it is not a good word but I leave that to you --

DR. CHILDRESS: We would welcome any proposals.

DR. SCHOOLER: I didn't doubt that. But the concern that I have is the concern of creating too many hurdles and that the, that in particular, many people, both with psychiatric disorders and not, that it is not a, as several people have said today, it is not black and white. It is not a decision you can make and then it is a decision done for all time. We have had situations where we were unable by our standards to approach a patient because we did not feel that they could understand what we were proposing in terms of the study and three weeks later could and did so we didn't approach the patient on day one, we approached him on day 21 and that is a very, it is a fluctuating kind of process and I would not like to consign someone to a label of decisionally impaired which then is a label that they are stuck with, in a sense, if that process is going to be fluctuating. I would rather have an assessment of it.

DR. CHILDRESS: Alex has a quick question.

PROF. CAPRON: I think your comments have been extraordinarily helpful. There is a double edged sword that operates with any of these labellings because the purpose of them is to provide extra protections but it also

carries with it the implication that someone else is going to make the decision for you, at least some extent of the decision. We also as a commission face a dilemma. We were cautioned by Dr. Cowdry not to make policy based on what are considered the worst examples or abuses that have been found or violations of rules.

I am also concerned that we not make policy resting on the best people in the field. One of my great concerns has been how can we or any oversight group know what is actually happening out there and we are trying to figure out how we are going to get to that level. The regulations and the implementation of the regulations and then the actual application in the field.

One thing that would be very helpful, and this is my question to you is have you, in any of your writings, addressed what you actually put in your budgets to have the level of support that you need to do the kinds of things, I mean, you go to drug companies and you say to them we need extra money for this wrap around funding. You probably also figure out for yourself that your research is more expensive to conduct because you spend more time on the consent process, you do all these tours, you contact the families as appropriate, et cetera, et cetera.

Have you ever costed that out? Because when we talk about barriers, one of the barriers to research that

we always hear is that will be too expensive to do.

DR. SCHOOLER: I am not an economist and my sense is that this is one of those operations where you lose a little on every item. I do not believe that we are being appropriately reimbursed for this. We argue with drug company sponsors that, as some of you may know, essentially these are called grants that they pay on a piecework basis that in some ways would put some old sweat shops to shame so that a patient who participates in a study for seven weeks earns X bucks for us, a patients who participates for three weeks earns less. A person who participates for three weeks is going to be more expensive for us because probably the reason they have only been in the study for only three weeks is they have not done well.

I have personally been unsuccessful in persuading drug companies that this is the case. The NIMH funded study that we had where we included a six month extension, that is sort of funded. In other words, that was put in as part of the budget. My read is that much of this kind of activity is always going to be borne by parts of the clinical system. I just don't think, I don't think any system can afford to pay for it.

PROF. CAPRON: Then I have asked my question in the wrong way. You are saying that you have never been able to get the reimbursement for it but you know to a

certain extent the amount of effort that different members of the staff put in. This is 10 percent of this person's job and 30 percent of that person's and so forth. It would just be enormously helpful, since you have spent time and adjusted your process as much as you have to respond to your concerns about good information flow if you could tell us your sense. I mean, this would be probably something with a fairly large range but just some sense of what that process costs you.

I mean, there are other fields in which I have been one that has argued that certain expensive processes up front about advanced directives for end of life care are actually not only more likely to deliver care that is appropriate to the person but may save the system money because people are not getting treatment and wringing their hands not knowing what to do. It is standing by the bedside for weeks.

I suppose that one might find some analogy but even if it turned out simply to be more expensive, I would like to have some sense of what the ballpark of what the expense of doing a good process of recruitment and informing and the continuing monitoring of patient and subject, I mean researcher and subject on the same wave length. Are you aware of what you are doing, et cetera. It sounds like you do that very well. If you could just

give us some sense of what is involved in that.

DR. CHILDRESS: And you don't have to today.

PROF. CAPRON: If it were possible, I would love not only from you but from some other people who have made special efforts here to get a sense of the order of magnitude and then multiply that times the number of studies and so forth. What would it cost the system that is spending billions of dollars to develop pharmaceuticals to do something in that area? More billions or more millions or tens of millions or what? I would have no way of saying it now but if you could help us, thank you.

DR. EMANUEL: If you knew the hours per patient.

PROF. CAPRON: But some of this is nurses' hours, some of it is doctors' hours, some of it is psychologists' hours and so forth. Some sense of that would be wonderfully helpful. Thank you.

DR. CHILDRESS: We will look forward to receiving that and we thank you very much for your presentation. Will you be around? For example, at lunchtime, maybe there will be questions that people would like to raise with you. Thank you again very much.

DR. COX: Can I just make a quick comment as my only attempt to answer Alex's question? The cost, it would be billions of dollars if they didn't have the patients to develop their drugs on and many of them are presently

recognizing that point and are extremely interested in having this particular issue resolved very clearly because they see not incremental cost, they see that it is an absolutely rate limiting step to them doing business.

PROF. BACKLAR: I think it would be also important for us to have a little picture of Nina's work outside the hospital, for patients who are non-hospitalized if that is possible.

DR. CHILDRESS: All right, okay. Thank you. Our next speaker is Professor Adil Shamoo at the University of Maryland at Baltimore School of Medicine and he is a spokesperson for Citizens for Responsible Care in Psychiatry and Research which is located in New York City. Now, you have a copy of his testimony. It was passed out yesterday and as he notes, there is some overlaps with his brief public testimony which he gave back in January if I recall. Because that presentation was brief and the time for sustained interaction was quite limited, some members of the subcommittee suggested inviting him for a more thorough interaction.

So I hope the fact that you had that testimony before and we have you paper will enable you to make very brief comments and then give us more time to raise questions.

DR. SHAMOO: I will try my best.

DR. CHILDRESS: The point was raised that people who were not here yesterday did not receive copies of your testimony so we will make sure everyone else has it.

DR. SHAMOO: Thank you for inviting me back. I will not go over my background in detail. Just two issues. One, I have been an advocate for human rights of patients and I have written in scholarly journals on the subject. But also I have recently in the past six months been the president of Howard County Mental Health Authority which we have the responsibility of health care for the mentally ill in the public sector. So therefore I am involved in the whole range of services and advocacy to the patient.

Research provides the only hope for parents of mentally ill and it is that fact that makes them more vulnerable. They are emotionally exhausted. It is worse than death because death has finality. The seriously mentally ill has no finality so they are financially bankrupt and emotionally exhausted so that makes them more vulnerable, them and their loved ones, to research practices.

I believe we have provided, in the past six years, sufficient individual examples of abuses in the psychiatric research. To you or other organs to investigate what has happened in the past 30 years. This is important because you are receiving information from the

research community. Today's, this is all from research institutions, representatives including myself, I come from research institutions or bioethicists works for research institutions. What you need really I think, and my belief is to go into the medical records of patients in a week or two weeks during which they signed informed consent. If they have, if they are in any shape or form they can sign informed consent.

My prediction would be that over half of those patients were not capable of comprehending what they were signing and therefore, and I am not an attorney but as a layman, I believe they have violated one of the cardinal rules of informed consent and therefore it was probably fraudulently obtained. Otherwise, talking to even organizations representing the patient, that is not sufficient. The Tuskegee and the radiation abuses were discovered by individual cases and reporters, were not discovered by peer review scholarly work and the information you are receiving and I will give you two examples. The psychiatric research community and their leaders and they continue with their massive resources to suppress, impinge on the integrity of those of us who have brought it before you and I will give you two examples to illustrate that because the quality of the information you are receiving today and subsequently in my estimations are

painted by that kind of behavior which in my view is unethical.

Two years ago I organized an international conference in ethics and neurobiological research with human subjects in Baltimore, Maryland. There were over 40 speakers. It was the most inclusive conclave to all the other NIMH and psychiatric research conferences. It was the most inclusive. We had 12 psychiatric researchers, two former directors of the National Institute of Mental Health. The American College of Neuropsychopharmacology which you have heard how receptive they are and the NIMH, how receptive to their view, issued an official boycott to their members who worked for our speaker to boycott the meeting. They were in the process of disrupting and basically canceling the meeting. Thank God that did not succeed and these are the proceedings just appeared recently. Ethics and Neurobiological Research with Human Subjects.

The second example I will give you is that I published, I submitted a paper, survey of the entire psychiatric schizophrenia in the entire world and I submitted that paper to the Journal of Clinical Ethics. I have been in science for 30 years. I am an editorial board member of numerous journals. This has never happened to me.

At the page proof stage, my paper was stopped from publication. The publisher was threatened by psychiatric researchers with a lawsuit if they published my paper.

The paper was resubmitted and it is now out in Cambridge Quarterly on health care ethics. The account of what happened to my paper was published in the professional ethics report of the AAAS and I will advise you to read it even with the rebuttals of the publisher and the editor in chief of the journal which basically confirmed every fact that I have submitted. This is published. It is no longer just a newspaper report or an oral report.

Let me continue a few things. I support research with human subjects because otherwise you will have an uncontrolled research trial, the patients and their families will use medications without any clinical trials. That is worse danger than really almost the abuses. Now we see. So I do support however, can and should be done in an ethical manner. The basic principle ought to be that decisionally impaired individuals should only be used as research subjects when it is in their best medical benefit. Only under extreme, unique and rare circumstances should we use this population for research without direct medical benefit to them. We should not design disguises such as advanced directives in order to use mentally disabled people in research.

Let me just quote you those who rebutted my article even. Edmund G. Howe who is the editor-in-chief of Journal of Clinical Ethics, what he said, and I quote. I consider the problem he addresses, referring to me, regarding research

involving patients with mental illness and particularly those with schizophrenia among the most important in medical ethics. The first problem, his study highlights is when if ever these patients should be taken off psychotropic medication or have it reduced to determine whether an investigational drug would be of greater benefit. This question is extraordinarily important because whenever these patients become ill as a result of their medication being withdrawn or if it is not being effective, their suffering is greater and substantially greater than that of most other patients.

The second problem highlighted is the need to find the best way to obtain these patients' informed consent. This question is critical because it is the patient's capacity for self-determination that is affected by their illness. End of quote.

Persons with serious mental illness, ladies and gentlemen, have by their illness been tormented, experience excruciating pain and seen and been in hell numerous times. I am a father of a son with schizophrenia but he has never been a research subject. They certainly do not need any additional pain and suffering in order to alleviate someone else's pain in some distant future and I won't go through my study and others who have shown that the relapse rate in the current research practices is if the withdrawal of medication is even done slowly, tapering off, which they don't do, to be perceived as

compared to what I called cold turkey sudden withdrawal is up to 50, 60 and sometimes as high as 80 percent, depending on what is studied. If they are on medication, the relapse rate is only 10 percent.

Let me remind the commission that the Tuskegee research team did not notice any evidence of widespread ethical problems for over 40 years. When abuse is committed toward the politically powerless, the uneducated, the poor, the mentally disabled, of course you do not have evidence for ethical problems. Certainly the abusers of the past were not and will not be committed towards doctors, lawyers, Ph.D. holders, corporate executives, academicians or VIPs. However, how much more evidence do we need, the Allers family, the attempts to silence them, my survey of published literature, the attempts at silencing me, documented suicide of Susan Andersby and where the basic fundamental principles of informed consent were consistently violated.

The violation of Shalma(?) Prince's right of treatment at University of Cincinnati Hospital, Ohio, the cries of Janice Becker about her daughter, the agony of Pastor Werner Lange of Chardon Falls, Ohio, about his brother suffering in research. The admission of leading government researchers or government-supported researchers that they inject street drugs such as cocaine and amphetamine into patients. The survey of Gilbert et al. that I cite and the horror stories documented by the TV

versus New York Office of State Mental Hygiene and recent course.

How much more evidence do they need to convince them? Remember, these psychiatrists are using a group of individuals who have no recourse, no access to independent monitors, review boards, lobbyists or policy makers. They cannot speak for themselves or defend themselves against abuse or exploitation. No wonder these researchers have enjoyed immunity for over 30 years and I would bring one more piece of information to you, and this is being revealed for the first time.

My survey of third year psychiatric research and, as all of you know, schizophrenia patients have the highest rate of suicide. Ten percent in a lifetime, a lifetime observation of 10 years, that is about one percent a year. Thirty years of research with schizophrenic patients with thousands of patients, how many suicides have been reported? Zero. The British study, equivalent study, they have the one percent predicted. Now, I question that those who committed suicide, most likely they were considered dropout so there is an issue not only of medical records keeping, the integrity of those research data in my view I question.

If the psychiatric research community and the National Institute of Mental Health claim that there are, there has not been any violation of any standards, why then don't they provide American people with the following information?

One, copies of all research protocols on wash-out and challenge experiments for past 30 years and copies of all informed consents. Of course, patients' identifications deleted.

Two, the fate of all those who participated in research and the fate of all those who dropped out of experiments.

Three, any suicides that occurred during the research protocols. The people of the United States, the taxpayer, have the right to ask and the psychiatric research community and the NIMH have the duty to provide information requested. And I thank you.

DR. CHILDRESS: Thank you very much. One of the questions obviously we have to address is how we balance the interest in research that is promoting research which you indicated is very important with the protection of research subjects and you suggested a few things along the way and I just wonder if you could, you indicate the advance directives should play no role. You made certain argument about certain risks that shouldn't be accepted, particularly with wash-out studies and the like but the one I want to raise is you say that I take you to be saying that unless the research has the possibility of the right benefit for the patient, subject, then you shouldn't proceed with the research.

DR. SHAMOO: I said, no, I left the door open. I am

not an absolutist and I cannot predict the future. I leave the door open and the unique and compelling circumstances, it is the responsibility of the principal investigator to convince the community were these researchers are coming from to convince them why he should use those patients in such high risk experiments which they derive no medical benefit.

DR. CHILDRESS: Okay, I have Larry and Trish.

DR. MIIKE: First I want to thank you for getting the time lag complex out of my head. You have partially answered one of my questions which was you want to basically limit research to benefits for the research subjects but you leave the door open for as yet undefined unique circumstances but I am not clear whether in terms of the whole research process in terms of informed consent, et cetera, you think that they are adequate and that it is the application by the psychiatric community that you are unhappy or against.

DR. SHAMOO: It is both. It is both. I think the current regulations are not adequate. For example, we have aggregates for years. The enactment of National Human Welfare Act. It is the equivalence for over 25 years for animals and this way you don't have all these trying to plug the gaps where the common rule applies and doesn't apply. Why can't we redraft the whole thing all over again and do it correctly?

No matter what is the second is that application is terrible and the currently existing system of IRBs, the law

requires one member of IRB. Now, usually IRBs are about 20 people from the same research institute, their colleagues, their wives, their children and they are real buddies. Now, how could one community representative outvote, I thought in a democracy usually the majority wins. One out of 22, there is no way they could have an input really and usually they make sure they are someone who will not speak the whole time of the deliberation.

So the whole process is really geared to protect the research institution and their researchers, not to protect the subjects which are derived from the community.

DR. MIIKE: Am I correct to assume that in terms of the IRB, this sort of relates to the discussion with Dr. Schooler was about. When she was asked the question of IRB, it is sort of like throwing a hat in a ring. Would you favor a separate IRB for these types of studies as opposed to an institutional IRB?

DR. SHAMOO: Well, first, I don't think IRBs should be in the research institution. They should be outside the research institution and the majority of the members of that IRB should be from the community which is providing the human subject for that research, yes. So currently the way the structure is flawed and it has, only in academia we use conflict of interest as a built-in structural method of determining this. We in science have lived with it well for years and years. We think that intermingling, it is appropriate for everything.

PROF. BACKLAR: Thank you again for coming and talking to us in your fiery fashion. I noticed you have many negative comments but I would like to know what suggestions you might have other than the remarks you have made about the IRBs for ongoing protection, adequate ongoing protection for persons with serious mental disorders when they are in a research protocol.

DR. SHAMOO: Again, the current IRB, once they approved the product, they practically had nothing to do with it. They received only reports of adverse reaction and I have seen those adverse reactions because I sit there in other places where they conduct, by the way. I am on the board of directors in an organization where they conduct this kind of research and I am trying to get them out of it for the past few years and I haven't succeeded. I am one of those who receives those adverse reactions. Those adverse reactions are couched in soft terms all the time so you cannot tell what actually happened. IRBs have no mechanism of monitoring ongoing research. They are not financed, they are not budgeted, they are not staffed so therefore I would like to see IRBs or its equivalent to have a monitoring capacity, to have the capability of audit if necessary, to go unannounced and audit the research protocol if necessary.

So there are ways of doing research appropriately without hampering it.

DR. CHILDRESS: Laurie and Alex and then we will turn

to our last session for the morning.

MS. FLYNN: Thank you very much for coming and sharing your thoughts with us. I want to follow up a little bit on the statement you made that you are very concerned and would I think not wish to see patients participating in research if they have psychiatric disorders where there is no direct medical benefit.

The concern I have about that, understanding certainly some of the concerns you have about abuses, the concern I have about that goes to the fact that so much of what we have learned in the past decade about serious mental illness comes really from very basic research, from research that really is getting a window into the living brain, looking at the difference between the brains of individuals who have these disorders and those who do not.

I think in almost every case that basic science, that basic neuroscience if you will is investigatory, is designed to expand the base on which future studies of more clinical or direct application will be made but doesn't bring direct medical benefit and yet from my standpoint, like you a parent of an offspring with schizophrenia, is that those studies have been critical.

How do you see basic science and neuroscience fitting into your concern about protecting human subjects with schizophrenia where there is no medical benefit directly to them?

DR. SHAMOO: Well, you noticed my comment is that I leave the door open. Let the investigator justify to the community why this research is being done. Now, there are ways of doing ethical research also with sufficient animal experimentation you have predictability of the drug, you have early intervention, the placebo is not necessarily should be done the way it is done now, up to a whole year waiting and watching the patient suffer so there are millions of ways, and I will be glad to sit with anybody, design an experiment where those ethical concerns can be alleviated at the same time the research could go on but I want to put the burden on the researchers at NIMH. They convinced the community why that research should proceed.

So I am not in disagreement with you. I would not close completely the door.

DR. CHILDRESS: Our last question, comment will come from Alex.

PROF. CAPRON: You make reference to this interesting gap in the data that you have looked at in terms of your supposition that there were suicides among subjects and they were simply treated as dropouts. Clearly that is a very serious charge and it seems to me one which I suppose a certain way it is incumbent on the research community to answer but it also seems to me incumbent on you to provide something beyond a mere speculation. There are, immediately one thinks of the death in

the UCLA study and I think that must have been reported if there was a death but maybe it would be interesting if the research results didn't acknowledge that but is there any way in your reporting you have been able to dig into any of these studies because the notion that you, your own suggestion strikes me as impractical.

You say what you expect NIMH to come up with is an accounting of all those people, what happened to all of them over 30 years. Well, if the researchers at the time were not keeping records of them as dropouts and certainly in at least some of the cases, I would suspect that the risk would be that a person really would be a dropout because they were getting increasingly psychotic or something and then they may well have committed suicide or they may have been taken by their family back into an institution and gotten treated. They were truly lost to the researchers and it may not have been responsible behavior but I don't know how you could expect NIMH after 20 or 30 or even 5 or 10 years to provide data on those people so that doesn't seem like a useful answer to this.

I am really, I am trying to grapple with what seems to me a serious charge and say how would we be in any position to react to your recommendations without some substantiation and yet I don't want to brush the charge aside either.

DR. SHAMOO: Let me preface so that we will put it in perspective. Now, remember all my efforts and those of my

colleagues are financed by our pocket. NIMH and/or anybody else has not funded any research towards what we think are the improprieties and they should look into it.

Second, let me give you the data versus speculation. I have data, accepted for publication in a peer reviewed journal what I have quoted. That is, the probability and I can't give you the name because they may go on again and stop this publication like they did before. This is not paranoia, this is reality in my case. The probability that all U.S. studies, statistical epidemiologists have done the work with me. The probably that all the American studies, the U.S. studies have zero suicide as compared to the British study which is the nearest to our culture and the research protocol is the closest to our methodology, the probability is 1 in 500. That is the data would indicate.

So it is small. And therefore, now I am going to speculation. I am jumping now, no more data, okay? I would be interested in somebody going into and look into it, were these suicides not reported? And if I have to do a guess as an advocate now as someone who is trying to impact public policy and I don't have the resources to do the research to find out actually what happened to these people, I will speculate yes, there were suicides and they have gone unreported.

DR. CHILDRESS: This leaves a challenge in still trying to explore further. We would appreciate, and actually

this is for everyone who has presented today, any written materials at any point that people would like to provide we would be glad to receive and Dr. Shamoo, thank you very much for sharing this with us.

PROF. CAPRON: For those of us who have been looking on colleagues' copies, could we get a copy of the testimony that apparently was distributed yesterday? Dr. Shamoo's testimony was apparently distributed to people yesterday and Trish and I didn't get it.

DR. CHILDRESS: That also raises something important because Dr. Appelbaum's, in addition, Dr. Appelbaum's and Dr. Shamoo's were provided yesterday so does everyone have a copy of Dr. Appelbaum's?

What we will do is plan to stop at about 10 after or a quarter after, have lunch for about 45 minutes and try to reassemble at 1:00 at which time we will take up the last topic for the morning which is the plans for the report in this area and then turn to Alex's proposal and then the rest of the time on plans and priorities if that is acceptable to the group as a way to proceed.

Dr. Appelbaum, thank you very much for joining us. Dr. Appelbaum is a distinguished professor and director of the law and psychiatry program and chairman of the Department of Psychiatry at the University of Massachusetts Medical School. He has done work over a number of years focusing on issues of

competence in the context of informed consent and the materials that most received but not everyone referred to research that he is currently conducting about determination of conflict in the context of research. Thank you very much for joining us today.

**Agenda Item: Continuation of Discussion - Dr. Paul Appelbaum**

DR. APPELBAUM: Thank you. It is a pleasure to be here with you and I appreciate your very civilized, informal dress code for the meeting.

I am, as Jim Childress just told you, a psychiatrist who plays many roles and some who has done research with human subjects although not interventional research for more than two decades. I am someone who has, as chairman of the Department of Psychiatry overseen the research of others including interventional research. I have served on IRBs and probably most directly pertinent to my discussion with you here this morning, for the last roughly two decades, I have been engaged in a series of studies with a number of collaborators on the informed consent process both in treatment and research. In particular I have a special interest in the whole notion of competence of consent in treatment or research and had a, as I will tell you very shortly, I have been involved in research on that issue as well.

My most recent collaborator in the last decade, one I should acknowledge here today, is Tom Brisous, psychologist at

the University of Massachusetts Medical School, with me and much of the work I will be telling you about we have done together.

Our research in the last decade has been based on our understanding of the element of competence to consent, either to treatment or to research, an understanding that we have derived from our review of case law, statutes, and commentaries in the legal, bioethical, medical psychological and philosophical literatures. We understand competence to consent to treatment for research, to refer essentially to four elements.

The first of those is the ability of the patient or research subject to evidence a choice, to indicate whether or not they desire to participate in a research project. Second, whether they can manifest an understanding of the relevant information which information is relevant is something I want to get back to later because that is an unresolved issue in our field.

Third, whether the research subjects have an ability to appreciate the implications of that information for their own situation, not merely being able to recapitulate what has been told to them but actually to understand that it applies to their situation and so many years ago, in a research project we were conducting on consent to psychiatric research at the University of Pittsburgh directed by Lauren Roth, then my colleague, we ran into patients who were able to tell us quite plainly that placebos would be used in the study and whether or not they got

placebo or active, whether or not placebos or active medications were assigned to any patient were simply a matter of choice like drawing out of a hat you might say.

However, when we asked them how their medication would be decided, they paused, looked confused for a second and then said to us, well, certainly I will get whatever my doctor thinks is best.

That is the distinction we believe between understanding what has been told to them which many of these very bright patients were able to do and appreciate what that information had for their own situation. It was from that experience that we coined the phrase therapeutic misconception to describe the phenomenon that we think goes well beyond psychiatric research and might be prevalent in research generally.

And finally the fourth element of competence to consent is the ability to rationally manipulate or reason about, if you prefer, information that has been communicated to the research subject.

Now almost all jurisdictions in this country and many jurisdictions around the world today identify one or more of these four elements as part of their standard of competence to consent but it is quite typical for any jurisdiction to have a somewhat unclear situation with regard to the standards. Standards are often developed in case law rather than by statute

and the cases tend to be responsive to particular factual patterns leaving you uncertain in any given state whether the different factual pattern might arise, the courts might broaden the standard. But in our research we have used all four of these elements of a compound standard of competence.

After conducting with support from the MacArthur Foundation's research network on mental health and the law, a large scale study of competence to consent to treatment in psychiatric and medical patients, we developed an abbreviated form of our research instrument and then further developed and transformed that instrument which we called the MCAT, the MacArthur Competence Assessment Tool, into a version that could be used to assess competence to consent to clinical research. There is also a treatment version of it.

The MCAT provides to our way of thinking a framework for systematic assessment of competence-related abilities and among the materials that Professor Childress referred to was a draft manual of the MCAT for you to take a look at. It can be individualized and should be individualized for each research project for which it is used. We have demonstrated that it can be administered and scored reliably and it yields indications of areas of impairment without being meant to provide the ultimate determination of legal competence of incompetence which I would maintain should never be solely the function of a score on our test or anybody else's test.

To date, we have done three studies in collaboration with three different steps of researchers. Applying the MCAT CR version, clinical research version to the psychiatric research setting, and let me tell you briefly about the results of each of these three efforts. I think they are instructive.

Together with Codnick(?), Hogue and colleagues at the University of Virginia, we looked at 28 schizophrenic research subjects on the research unit there and they recorded 24 matched controls. They used the hypothetical medication study as the basis for the instrument, the questionnaire and found significant differences on all elements between the research subjects and the matched controls, matched on age, socioeconomic status, gender and race.

Moreover, 67 percent of the schizophrenic subjects scored below the lowest control, member of the control group, on at least one of the four scales, the four elements. A study that raises although the sample is small to be sure, at least some questions about the degree of capacity that many schizophrenic potential research subjects may have.

Will Carpenter and his group at the Maryland Psychiatric Research Center have been collaborating with us on an additional study of 30 schizophrenic subjects of whom they found more than 50 percent appeared to be impaired, that is, fell below a priori cutoffs on our instrument. They correlated this impairment not with psychiatric symptomatology per se but

with a battery of neuropsychiatric measures that looked at cognitive functioning. But, and here is I think a particularly interesting data and reflects back on the Virginia study as well. Following an intensive educational process on 10 of those 30 subjects, they found that 8 of the 10 now scored very well on the understanding measure when it was readministered. In fact as well as the control subjects did on average in the Cognick, Hogue and colleagues study in the University of Virginia.

The third study was done in collaboration with Ellen Frank, David Kupfer and their colleagues at the Western Psychiatric Institute Clinic in Pittsburgh and looked at 26 female outpatients with moderate depression who were recruited into a long term maintenance phase study. In that population, we found almost no impairment on understanding measures and only one or two subjects who demonstrated any degree of impairment on appreciation or reasoning. When retested eight weeks later, there was little change on average in their functioning.

The messages from these preliminary studies, and I really do underscore the fact that they are preliminary and they use small samples are, I would submit, the following:

First, this instrument, the MCAT CR seems to be a reliable and from all appearances valid way of measuring patients' capacities related to competence to consent to research. Second, the studies clearly demonstrate that psychiatric patients as a group are not a group. They are not a

homogeneous sample. They have different diagnoses and within diagnoses have different degrees of impairment and when we talk about decisional impairment, not a term to which I object, I would only hope that we recognize that impairment exists on a sector and what is not impaired or not impaired, one is impaired to varying degrees. I suspect we are all impaired to varying degrees, particularly when somebody gives us a seven-page single spaced consent form to review and stands there waiting and tapping their toes as we are looking through it knowing that they expect us, given the social context of the situation. Perhaps previous commitments that we have made in fact to sign on the bottom line.

But the impairments are not randomly distributed, based on these preliminary data and certainly on the much more extensive data we have from treatment settings, on depressed patients in general appear to be much less affected by decisional impairments than to schizophrenic subjects. We have not yet studied other groups but bipolar patients are an obvious group to look at and one can speculate that they may fall somewhere in between.

Moreover, the preliminary educational efforts in Maryland suggest that even subjects who fall below what you might construe to be minimum standards when initially given information and then soon thereafter tested on it might, with repetitive educational efforts, come to the point where they

can, in fact, understand that information and what remains to be evaluated is whether they can appreciate and reason with it as well.

And finally I would say that these preliminary studies show us that even severely ill populations show a range of performances and it would be just as improper to consider all persons with schizophrenia to be unable to give a valid consent to research as it would be to generalize that more broadly to all patients with a psychiatric diagnosis. To the extent we can identify risk factors for poor performance which several groups including we have attempted to do with variable results I must say, we may be able in the future to identify the high risk subpopulations within those groups and make special efforts with regard to them. But the range is there without a doubt.

Let me conclude, as Professor Childress asked me to do with some thoughts about the implications of some of our work for the policy issues with which you are and will be struggling.

First, there is no question that the dilemmas related to involvement of patients with impaired capacities are real and warrant careful consideration. We have seen at least important indications of significant degrees of impairment in a number of the groups that we have looked at but, of course, the benefits of research are real, too, and some way of weighing these two imperatives must be found.

I would submit that as far as dealing with impaired

populations are concerned, we are not at this point ready for sweeping new regulations and new approaches and I say that because I believe that several steps are necessary before we get to the point of mandating new procedures and new approaches.

First, we as a society need to agree on the criteria we will use to determine whether or not somebody is competent to consent to research and insofar as possible, the cutoffs on those criteria. This gets back to the question of how much information people should know, how well they should be able to appreciate its implications, and how clearly they need to be able to reason before we will allow them to consent to research or deprive them of that possibility.

Second, we need to establish that we have effective means of identifying impairments on those capacities. I proudly told you of the work we have done on one instrument but it is just one instrument, it is preliminary work, it sure would be nice if other groups besides we in our collaborators could demonstrate the reliability and validity of this instrument and it is not yet ready for prime time in the sense of being mandated by anybody to be used on a large scale.

Third, once we have such instruments, we need to use those means to identify high risk groups so that we can target our protective efforts in as focused a manner as possible. The targeting of additional protections, whether they are educational efforts or efforts to monitor the consent process or

others addresses in part the issue that Professor Capron raised earlier about the resources that are necessary to accomplish some of these goals.

To the extent that we generalize our protective efforts across all patients who have diagnoses that may involve decisional compromise, you are talking about an enormous enterprise that will cost a great deal of money, time and effort. To the extent that we can target those efforts on those groups most likely to benefit from them, we are likely to be able to do that in a much more efficacious manner.

Fourth, I would say we need to explore the mutability of these impairments as Will Carpenter and his colleagues have started to do down in Maryland. Merely identifying people as having decisional impairments does not mean that they are incompetent to consent to research, treatment or anything else. It means that they are at high risk for being incompetent or lacking competence but that risk may be mitigated by additional efforts made by us, whether they are educational efforts of the sort that Nina Schooler described to you, whether they are efforts to provide a more congenial setting and supports of family, friends or trusted confidants to enable them to think through the dilemmas with which they are faced or other efforts.

Then, when we have taken these four preliminary steps, I think we can talk seriously about making sensible policy in this area. What do we do in the meantime, though? These

studies are going on and if we are not to suggest immediate new regulations or legislation, how do we protect the subjects who are in these studies right now? Well, I would suggest to you that we know enough to encourage investigators and IRBs on their own to begin taking some quite reasonable steps that would take us down the road toward greater protections.

We need to encourage IRBs and investigators even in the absence of a societal consensus on what constitutes competence and what the cutoffs should be to develop their own criteria and their own approaches to this issue. It is meaningless for investigators to assure their IRBs that they will not enroll any incompetent subjects in their research studies if neither the investigators nor the IRBs understand what criteria should be applied to determine incompetence or where the cutoffs should be made.

That is something we can begin to do using IRBs and the investigators as, in a Brandeisian fashion as the laboratories of the states in a decentralized way and gain experience that can then rise to the national level where a more definitive policy can be made. We need to encourage them to develop assessment mechanisms of the type that Dr. Schooler and other investigators are beginning to use and have used in some cases for a decade or more.

We need to engage in training of investigators and above all of research assistants, the forgotten people in this

area. The ones who have the direct contact with the research subjects and potential subjects who do the recruitment who in many cases obtain the consents and conduct the consent transactions and who in a study that I did with Lauren Roth in the mid-1980s, we showed were left almost entirely without guidance in the sample that we looked at of 18 investigators conducting human research in psychiatric studies as to what to do with a subject who appeared to be confused and not understand the information that was being conveyed.

Then finally, at present I believe we could certainly encourage investigators to and IRBs to require them to document the percentage of research subjects who are being excluded from their studies on the basis of incompetence. If you are dealing with a high risk population, severely ill schizophrenics, psychotically depressed, actively manic potential research subject and you have conducted a study where you have recruited 100 subjects and excluded none on the basis of incompetence, I submit to you are not doing a very good job of screening your subject population and that unless five or ten or in some populations an even greater percentage of subjects are excluded no that basis, then you are certainly leaving yourself vulnerable to charges after the fact that competence is not something to which you have paid careful attention.

DR. CHILDRESS: Thank you very much, Dr. Appelbaum. I have Trish, Eric and Alex and Laurie.

PROF. BACKLAR: Dr. Appelbaum, thank you very much for your presentation. I have one comment and a question, the same question I actually gave to Dr. Shamoo and that is I was interested in one of your papers on your study that you talked about where you were doing informed consent, what seemed to work was to do it element by element and you didn't mention that. Maybe I missed this and that you also perhaps could tell us a little more about that process and how that seemed to work rather successfully because it seemed to me, and I may have misread it that you said just repeating it doesn't necessarily do any good and you seemed to contradict that today. So that was one point.

The other point that I would like to hear from you is how you are concentrating on consent, how do you see that one could improve the ongoing care during a recent protocol to insure that the patient is well protected from beginning to end and actually afterwards.

DR. APPELBAUM: First with regard to element disclosure, we found in our treatment study of roughly 500 psychiatrically ill, medically ill and controlled subjects that the psychiatric patients, both depressed and schizophrenic in our sample, in many cases manifested much more severe impairments of their understanding of information when it was communicated to them in a single bolus with all of the information required under the usual understanding of informed

consent to treatment given to them all at once.

Then if we broke it down into pieces and queried them after each component or each element of disclosure took place, I think that is more than mere repetition. I think that that is a modification of the way in which the information is presented that may, in fact, be helpful much more generally as it was with our quite impaired population. I thank you for calling that to my attention.

That, of course, goes along with the question of how much information we are giving research subject and I don't mean to sound heretical. I am of the view that we give research subjects much too much information and at the same time often the wrong information. Seven page, single spaced consent forms are not unusual. I reviewed this weekend several protocols that one of my investigators in my department is submitting to our IRB, one of which, well, they range from eight single spaced pages to twelve single spaced pages in the consent forms. And there was some important information in those forms but it was buried and I just had the discussion before I came here with that investigator about it, at the very least putting it in bold or pulling it to the top of each section so there is some way for subjects to focus on what is really important like the risk of relapse with placebo which was an issue in his studies as well.

So a focus on really the difference between research

and treatment seems to me to be much more important than any of the minor procedures or minor risks from those procedures that relay to the subject.

The second question you asked was about improving the process as the research goes along. I don't think disclosures ought to be something that takes place just at the beginning of a study. Talking to research subject who have been involved in longitudinal studies often reveals that two weeks out or two months out or six months out, they have a very fuzzy understanding of what it was they consented to in the first place and even if you were a conscientious researcher and gave them a copy of the consent form at the time and perhaps even additional educational information, the likelihood that I would be able to find something like that six months later with my secretary working valiantly to keep me organized, is small and I think for them it is much, much smaller and so continued education and re-disclosure over time, not necessarily reconsent in the sense of a formal process, let's go through this all again, but redisclosure and, of course, disclosure of subjects' rights to withdraw, should they so choose seems to me to be a very valuable addition to the usual procedures.

PROF. BACKLAR: It seems to me, would you consider these suggestions you are making something that would be applicable generally throughout the consent process with anybody who is in a research protocol?

DR. APPELBAUM: Yes, and not limited by any means to decisionally impaired people.

DR. CASSELL: I find your presentation very interesting and very important after you make it clear the deficiency in the process then you also make it clear that you are worried about more regulatory solutions to the problem. But this is not a problem that applies only to the psychiatric patient.

Many years ago, I did a bunch of tests using Piaget's tests for the concrete child and a pre-operational child on physically ill people and they routinely failed those. As a matter of fact, even people you think are entirely well three or four days post-operative will fail the test for the conservation of the horizon which virtually nobody fails who is healthy. So that the inability to make a judgment, that is a minor part of it but the inability to make a judgment is characteristic of illness. It is one of the, it is not regression, it is illness and in some illnesses much more than in others so we have come a long way from thinking that autonomy is what we thought it was 25 years ago in the first part and the second thing of thinking that consent is a simple matter of reading and then signing. anyway, for a solution to the problem of getting people to participate in research which they want to do, put it that way, which they want to do, so that they know what they are doing and know that they will be protected. That is a difficult set of

criteria to meet without vastly raising the complexity or the cost or something but also essential.

I actually think we will find a way to it. Dr. Schooler made one suggestion which we have discussed at other meetings which is the education of the investigator so that the investigator is also an educated person in this process but you can't just say we have found all these deficiencies or defects but regulation would be a bad thing today. If you found them, you found them. If they can't consent, they can't consent and then we have to solve that problem. And regulation is one way but not the only way. You just can't put it aside which I don't really think was your intent but that actually was the way it came across.

DR. APPELBAUM: That is not my intention. I wouldn't want it to come across that way. I have no objection to regulation in this area. Clearly we made great strides in the 1970s when we began developing human subjects. Regulation and we would still be in the wilderness had we not done so. I am concerned about the potential, given the degree of public interest in this issue right now for premature regulations. For regulations that specify things that we are not yet capable of doing or that assume that there are problems that we have not yet clearly documented are there. I think a process of gathering information first and regulating afterwards is likely to lead to much better rules that we all have to live with.

DR. CHILDRESS: Alex, Laurie and Harold.

PROF. CAPRON: I would like to just have you clarify your description of some of the work that has gone on. In the Maryland study you said that after the interventions there was an increase in understanding and then later on you said in passing, not specifically about that but I wonder if it was that study that we don't yet know what the effect on appreciation is. Is that being studied there and is there a basis for assessing changes in appreciation since your own earlier works showed that understanding by itself is a rather poor surrogate for an informed decision.

DR. APPELBAUM: Yes, the answer is that these are ongoing studies and in pulling together my presentation for you here this morning, I called our collaborators and said fax me your latest data. I need to synthesize it for the commission so what I got was data on the understanding of measures. There should be data as well on the appreciation and I am just not able to tell you today what they show.

PROF. CAPRON: And the more global question is the research projects that you have described are themselves studying the MCAT CR. They are not, as I understand it, studying the interventions. That is to say, is that a clear question? Is that correct?

DR. APPELBAUM: Yes, at this point that is correct.

PROF. CAPRON: So this is not yet research on the

question of how does one best make the changes, how does one best educate, what process works best. It is simply an evaluation of this instrument.

DR. APPELBAUM: That is correct. Although such studies as you are suggesting have been done previously. There is a small literature but it exists.

PROF. CAPRON: But these particular studies are not on that. Again, it would be helpful if you would be willing to aid the commission by providing some description of what you think the best studies in that other category are since you have written about it yourself, I assume this is a task which more or less involves downloading things that you have probably already done from your word processor but it would be helpful to have that.

MS. FLYNN: Thank you, Dr. Appelbaum. I have two questions. You made an a point I think we all recognize that the assessment competency is really a crucial aspect when dealing with subjects who may be cognitively impaired, particularly some as vulnerable as your research seems to indicate. Some patient with schizophrenia might be. It has been suggested by advocates and has indeed been endorsed by NAMI's board that one way to deal with the problems of potential abuse there would be to recommend that the assessment be done by a medical professional appropriately trained but who is not directly participating in the research itself so that the

potential conflict that may arise there would be potentially mitigated.

So I would be interested in your comments on that and in your understanding that concern that people have, particularly with those who are both vulnerable and may have fluctuating competency and the second sort of related question is given that we have all noted that the informed consent process is now so lengthy and in such find print that it takes a battery of lawyers to understand what it is you are being informed about in many cases and considerable time to make certain that individuals do have some working knowledge of it, that in the end it seems most of these legal forms tend to protect the institutions, not necessarily the individuals who are the subjects.

Would there be some value or could you give some guidance, would IRBs be able to draw from your work and some of the work you have cited what might be helpful models of informed consent or best practices in educating researchers and research assistants and engaging patients and others in the process? Do we have a body of knowledge that has not been collected but that could be brought together in a way that would enable an ongoing educational program that might raise the level of practice?

DR. APPELBAUM: First with regard to the question about having an assessment made by somebody outside the research team. I would raise a broader issue than that although it is

one that is very complicated and clearly very controversial among the research community. There are clear conflicts between being a researcher with a subject and being a doctor with a patient. It is not always possible for one person to do both.

And yet for a variety of reasons it has become common in our research institutions for one person to do both. I think it is worth some thought and I don't pretend to have the answer as to whether that is a practice that needs to be much more sparingly used than is now the case. Certainly in some studies where a treating physician is distributing questionnaires to patients and getting their opinions about side effects or the like, there would be little reason to worry about conflict of interest but where it involves recruitment of subjects for research that may place them at substantial risk, there are a variety of reasons I think including the social pressures of saying no to your doctor that may make it worthwhile to think through whether we want to be doing this quite as often as we do right now.

Your second question deal with whether there are models or best practices that we can draw from the literature with regard to ways of improving the consent process. The answer is I think there is a lot of information out there. Some amounted it generated in the research context but a lot of it is sitting in places that few of us routinely look like the educational literature, educational psychology literature about

ways of communicating information to people.

We know that for example smaller chunks of information are more easily assimilated than larger chunks of information and were we to develop consent forms that were limited to one page and had on it only the essential descriptions of the projects and the ways in which those projects differed from ordinary treatment and then, that was our consent form, that people had to read, understand and sign and then provided 8, 10, 12 or more single spaced or hopefully double spaced pages of information for them to learn more about the projects. I think we would have a much more effective communication process than what we have right now.

But yes, there is literature out there and we have under-utilized it today.

PROF. CAPRON: You might refer to it as project plain English to start off with.

DR. SHAPIRO: The problem I was struggling with really goes to Laurie's first question, the first of two questions she asked and your answer to that issue. I really am taken with the concern that one, it is difficult to diagnose. There is another specialized diagnosis needed here. That is, is someone capable of understanding? Do they have the capacity and appreciation and so on as you have outlined in the test that you have so carefully constructed? That is a new and specialized skill it seems to me that is on the horizon now and I tried to imagine

how to deal with that. It seems to me that almost inevitably you get the situation where you do have to take what you describe as a controversial step and you separate the recruitment from the treatment for example and maybe you can separate the recruitment form the research.

I know that is controversial, it came up earlier today in some other context. I have forgotten exactly the detail but I think that is worth some careful thought in my sense because it does solve, nothing solves this problem. I don't know what it will do. It may dry up the whole pool of candidates which is what I hear from the medical community very often and no one had any incentives to recruit anybody and then no one would be recruited to any medical experiments and we would all be worse off.

It is the kind of quick kind of answer I get but I don't know if that is justified or not. We don't have to pursue that but I think that is an interesting issue and have you also in your, you seem to indicate you have also experienced this to be a very controversial issue. You have obviously discussed this much more often than I have. It remains controversial. Do you ever convince anyone to change sides on this issue?

DR. APPELBAUM: I don't know that I have ever tried. The separation of the research function from the treatment function would probably obviate the need of the separation of the recruitment function from the research function because the

common book of interests would diminish.

PROF. CAPRON: I don't follow.

DR. SHAPIRO: The skills might not be in the same person.

PROF. CAPRON: If you had it evaluated, if I could just get a reading, if you could see by the physician-patient treating relationship where that is a patient and then the person is identified as a potential participant in the research, the notion at that point of having an independent evaluation of that person's capacity to understand the issues that would arise in being enrolled in the research doesn't strike me as obviated because you were then going to separate that role from the role of the investigator, him or herself who both conducts the research and has responsibility for the consent process.

I would also assume if this skill were developed, that the evaluator would be able to say not a binary choice, yes qualified, no not qualified but a gradation which would indicate what additional steps would be appropriate from saying this person doesn't have any capacity to consent so they can only engage in research that doesn't have any risk to them at all versus they have a lot of capacity but they really need a family member involved or a different process. There was a graduated scale that gives some attention but the way the doctors treat him now might send someone to an outside psychologist for a test or something. They wouldn't necessarily as a physician do the

test themselves.

It doesn't seem to me it is an either onerous or extraordinary step that we might consider and it removes the problem from all of us looking at the process saying how can we trust Dr. Jones administering this instrument when he has got a potential subject right there with him and all the inclination would be to subtly, subconsciously, otherwise come up with a result that would say ah, this subject is okay for mediators. I mean, just eliminate that as a conflict, as a suspicion.

DR. APPELBAUM: You certainly could do that. If you were looking for a more economical way of handling it both in terms of effort, time, construction, the bureaucracy to do it and the like. You could charge the treating physician with insuring that the patient in fact has the competence to consent to the proposed research and let that physician either do the determination him or herself or bring in someone else to do it but at least give them the option of certifying the individual's competence.

PROF. CAPRON: You don't mean the treating physician. You mean the investigating scientist.

DR. APPELBAUM: No, I mean the treating physician who is presumably there solely devoted to the patient's best interest at this point without conflict of also being involved in research.

DR. EMANUEL: I want to raise a concern about this

separation. One of the problems we know that happens when people go into research institutions is they don't know who the doctor is, who is responsible, and by separating things out you may fragment things and this could be a serious problem in this vulnerable population. As an oncologist I know. One of the things I worry about is when I refer patients to a research trial, the continuing of care, my understanding of their needs and concerns, their support structures, gets totally lost. There is a risk and a high cost I would suggest of separation.

I want to challenge you along these lines. You suggested you should be realistic and try to target the population because there is a spectrum but I suggest I want to challenge you in the following way. I suggest in point of fact to be realistic is we are going to create a pool of people by our definition of decisionally impaired and that the knee jerk or the simple thing for any IRB to do is to create sort of fairly high levels of requirements for people who are using those subjects or researchers who are using those subjects so all of them are going to have to get this battery of tests, an intensive educational intervention. That is going to, then the IRB is sure no one is going to fall through that safety net or if they fall through it will be pretty rare.

It seems to me targeting is the right motivation but in the practical sphere the immediate consequence for an IRB is going to be just the opposite. Once they are in a pool,

designated labeled as potentially decisionally impaired by virtue of their medical diagnosis.

The maximal intervention that we require are what they are going to necessitate. I think that, that is what my IRB would do I am pretty sure.

DR. APPELBAUM: Well, I wouldn't like to see that happen obviously because I think it would be a waste of resources and would put many obstacles in the way of the conduct of research and given the other accusation we have heard against IRBs this morning and which is frequently voiced, namely, that they are too friendly to research interests, one might expect that they wouldn't be tempted necessarily to move quite that far in that direction.

But that also goes to the question of whether this issue is right for discreet regulation as opposed to encouragement of further experimentation and maybe preliminary steps in this area. If we talk about decisionally, potentially decisionally impaired subjects, you are encompassing an enormous range of medical as well as psychiatric diagnoses and then if you start laying out regulations to cover that whole group, you are in exactly the situation that you describe.

On the other hand, if we have taken the time to identify who the truly high and perhaps moderate risk groups are within that much broader group, we can then give IRBs and investigators much more particular guidance as to who deserves

the extra effort, who really needs that extra degree of protection.

DR. CHILDRESS: Dr. Appelbaum, thank you so very much for joining us today. We appreciate this discussion. We will reassemble at 1:15.

(Whereupon, the meeting recessed for lunch at 12:16 p.m.)

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

DR. CHILDRESS: It has been suggested and I have agreed to an alteration in the order for the afternoon that will deal with Alex's concrete discreet recommendation first and then talk about the plans for the report of decision impaired subjects in the context of all of our projects and priorities. So unless there is any objection, we will proceed that way.

**Agenda Item: Lack of Data in Federal Research Oversight - Mr. Alex Capron**

PROF. CAPRON: I don't feel the need to repeat concerns that I raised in the memorandum. I think there are two concrete things that could come out of this. One would be to turn to the relevant bodies and ask them whether the problem as described and details by the President's commission in its exchange with them a decade ago, 15 years ago, remains or to the extent to which it has been addressed, and the second is to possibly identify a couple of people who would pay differing views on this question of achieving independence for the research oversight function from any particular department and agency and establishing it outside.

I was asking Jonathan as the meeting began to try to remind me whether the ad hoc committee had addressed very directly the history of the Atomic Energy Commission since the commission was the sponsor of many of the egregious research protocols that were discussed by the ad hoc committee.

The history to which I am referring to is the fact that it finally became apparent, not because of those research projects as such but because of other problems, that it did not make sense to have one agency playing the role of sponsor of research and regulator of the safety of that research and the result was of course the Department of Energy having the responsibility of sponsor. There are other government agencies that also sponsor research with radioactive substances but have the principle role that the AEC had played there as sponsor, taken over by DOE and a newly created Nuclear Regulatory Commission to be in with the safety issues.

It would seem to me by analogy that it must be very difficult to be a director or a secretary of any of the departments with substantial investments in research to also expect to protect your oversight office from the complaints that you hear from you exercised intramural and extramural investigators about how that office is making their life difficult and it would just be much more sensible if that responsibility were shifted out of the departments and so forth that have the very justifiable concern with supporting research and encouraging it, sponsoring it, paying for it into a separate office.

I would also expect that we could find a higher level of accountability from that office if it no longer had that constraint and its sole function would be the oversight and

improving the quality of the research oversight, educating IRBs, developing guidebooks, sponsoring research on the kinds of questions that we don't have all the answers to the kinds of questions that Dr. Cowdry mentioned, et cetera.

And so I would like to think about our commissioning then a couple of papers because this is not going to be a view that is met with enthusiasm from all quarters but as to the desirability and feasibility of separating out the function and establishing a separate agency. I guess another example of an agency that has a government-wide function, not so much an external function is the Office of Ethics which had been part of the Office of Personnel Management at first and now has an independent status so there are other examples that we could look to or that somebody informed about the federal structure could look to as to what is feasible and so forth.

MS. FLYNN: Alex, I am going to confess that I have not read your paper. I can't even locate your paper.

PROF. CAPRON: It is under tab C in the book.

MS. FLYNN: I don't have the book. That could explain it. I don't have this book because I wasn't here yesterday. Can you --

PROF. CAPRON: This was mailed.

MS. FLYNN: I understand probably it was. Can you just ---

PROF. CAPRON: Unlike the stuff that wasn't passed

out.

MS. FLYNN: I have already confessed that I have somehow neglected to read your paper. Could you just in four or five sentences tell me what the core proposal is so I can, I have been listening to what you have said and I think I followed it but I didn't quite hear what the core proposal is that you are making.

PROF. CAPRON: My observation was that there was the report in the New York Times in May about the fact that we don't have data on the number of research subjects, the number of projects and the types of projects that are carried out on human beings although we have that data on animals and I was simply saying that I thought it would be worthwhile to remember that this is not really news and that in 1981, in its first biennial report, the President's commission recommended that all federal, and I am reading now from the language of that report, all federal departments and agencies that conduct or support research with human subjects should require principal investigators to submit as part of their annual reports to the IRB and the funding agency information regarding the number of subjects who participated in each research project as well as the nature and frequency of adverse effects.

And there were other reports from the President's commission noting that that information was not available. We have spoken briefly as a commission already about this problem

about the adequacy of the information. It seems to me that it is of particular urgency, I tried to argue for us to get such information, for such information to be available if we are thinking as we already have tentatively decided to recommend that the protections of the federal system be extended to all research, whether or not federally supported and, of course, the Glenn bill and there may be pending legislation I guess on the House to do the same thing.

If I were a member of Congress critically examining that proposal and it was being told by people in the private sector that this was an unnecessary burden being imposed upon them, I would expect to be able to compare the rate of problems in federally funded research with the rate of problems in privately funded research and we certainly have had examples and that article in the New York Times mentions them and others, we have heard from Dr. Ellis, exist of privately funded research that has problems but that is maybe part of the numerator but we don't have the denominator there but what is more remarkable is we don't have either the numerator or the denominator for the federal side.

So it is hard to make the assertion that research that is federally reviewed has fewer problems than research that is not and since we are likely to be making a recommendation in that area, it seems to me we need such data.

So what I was saying was let's first find out by

asking the FDA and OPRR and so forth, whether the observations made by the President's commission both in the 1981 report and then in the 1983 report are in some ways outdated because indeed there have been steps taken which address the concerns raised there and then to the extent that they haven't been, become outdated by later improvements, what is their response to this underlying concern that the data are not there and what efforts have they made in evaluating how difficult it would be to get the data or what problems they have run into in trying to accumulate the data and so froth so we can be in the position to comment on it.

That is topic one. Then topic two is the one I addressed at a little greater length just now saying the basic question of whether OPRR and its counterpart agencies in other departments should be the sole means of protecting human subjects seems to me to be right for discussion and the idea would be to get a couple of people with differing perspectives to write a short contract paper, come and sort of debate the topic with us as to whether or not it would be desirable or not desirable to create that function as an independent, government-wide function, not dependent upon the secretaries or directors of departments and agencies and divisions and institutes and so forth for its existence since those groups have a strong commitment to the research side.

Two topics, each one requiring some action.

DR. CHILDRESS: Are there any questions on the proposal as stated?

DR. COX: If you think your second proposal is unpopular, wait until you hear about this one because I think that it is a really interesting opportunity to rethink this but why do we limit ourselves to the case of federally funded stuff? I think that in some ways this artificial division between the private sector and the federally funded sector and there is a whole variety of organizations out there representing the private sector that want this information even more than the people in the federally funded sector do.

So I think it is a golden opportunity not only to collect what the common rule says right now in terms of federal agencies which is what our staff is doing but to inquire about the interest of other people collecting similar information in the private sector but then my suggestion, Alex, is that one then consider, I endorse having such papers prepared but I would expand the potential scope to think about having a national place dealing with both private and public human subjects research that would be a clearinghouse for us.

Now, I know that sounds nuts but I would be interested to hear what the real impediments to such a thing would be.

PROF. CAPRON: It seems to me that would be combining the idea in the Glenn bill and our own in principle endorsement that we came to during the process of the report for insuring

information for all subjects with this other suggestion. It would seem to me in that context that it would be much more sensible if that were a government-wide office. That is to say the notion of the Pharmaceutical Manufacturers Association members, I guess they actually have Pharmaceutical Manufacturing and Research Association.

DR. COX: There is Pharma, there is BIO, there is a variety.

PROF. CAPRON: I am just thinking of those members as being an example of the groups that you described that have a very strong desire in seeing biomedical research go forward and they sponsor a lot of it, that it would make more sense if they were reporting to an agency that was not a sub-sub-agency. I mean OPRR is now --

DR. COX: Listen. So I think it is a non-starter for them to be able to report to a government sub-sub-agency. I actually think it is a non-starter for them to report to a, quote, governmental agency but we can have an overall national agency. This is what I am not sure about how that works, especially the public private partnership in dealing with human subjects research and there are other models. Like in Canada, about how that is done. I am not saying that we are Canada. I am not saying we are Europe but there is ways that it could happen.

Now, the reason why this is extremely unpopular or I

anticipate that it will be extremely unpopular is because that is not how the administrative world is cut in our country. Our world is cut private and public but if I think our commission isn't that way. Our commission is set up to talk about human subjects research in our country and so maybe if --

PROF. CAPRON: Actually, if you read our charter that is, I think, a misstatement. The charter always struck me as unusually focused on federally sponsored research. It basically says the issues that arise from federal sponsorship of research. I don't think that ought to restrict our sort of blue-skying this issue and I would certainly think that the notion of having a third contract paper not just yes, no on government-wide and moving it out of the departments but more broadly asking the question is this something that could be conceived of in that public-private partnership realm would be great if there is something for someone to talk about in terms of other models and other countries.

DR. COX: There are other models in other countries.

PROF. CAPRON: I think that would be very informative and I would support the addition of such a study and report back to us as part of that undertaking. But I just don't think this is a topic that we ought to just let slide by wringing our hands at the role conflicts that we have talked about earlier that arise. I think they arise even at this regulatory level.

DR. COX: Having said what I did, let me say that as

keen as I would be on an (word lost), if we couldn't bring the private sector into it, the idea of having then even a higher level one that makes a clear distinction between the federal research subjects protection and the private, I think may not be as helpful as it otherwise could be because it makes for these very clear sharp dividing lines between public and private and in humans, although Harold made really good arguments about why that may be a good distinction for how you decide how you fund research, I think it provides an awful lot about how you decide to take care of human beings.

DR. EMANUEL: Alex, it seems to me one issue is sort of regulatory issues that we need to think about and the idea of commissioning papers is to fuel our own thinking and debate. The other, it seems to me, is a, in some ways, a much more substantive questions and it helps in two regards. One, it seems to me it would help us collect data and information that we repeat in this area over and over and it seems to me now 16 or 20 years and we just don't know the answers to these questions even though everyone agrees the answers are important and B, it shouldn't be that taxing or difficult at the end of every research grant to get a report back just like you have the number of people who participated. What your response rate was in the study. This is what happened, X number of people died, X number of people had adverse effects and X number of people had nothing.

I mean, that does seem to me, I mean, first of all, in the absence of data people don't have any idea what is happening and it is pure assertion and the presence of data I think is likely as many people in the research world know, likely to get the number of side effects, probably to be reduced because people are finally paying attention to those numbers.

I want our ability to actually require that or we certainly have an ability to suggest it.

PROF. CAPRON: I guess what I was saying was that before we get to the point of suggesting it, I would like to hear back from the agencies most involved and responsible, namely the FDA and OPRR within HHS, whether the landscape has changed since prior groups have said we need that information. And I don't want to repeat earlier recommendations and then have people say this or that aspect of them is no longer applicable because we have changed this or we do have data on that or we have a regulatory, let's just get updated.

I mean, this is the kind of thing which frankly in certain ways I was more, it was more that we were about to have a meeting in June when I wrote this on May 30 that made it seem sensible. I would otherwise probably have simply sent this to Harold and said why don't you in your role as chair make this query to these agencies and you as chair, we don't really need the whole commission to endorse you doing it.

We then add a human subjects subcommittee scheduled

for June 7 so when I sent the memo I thought, well, we can get the whole committee to talk about it briefly and it is such a sensible proposal that we will all endorse it and Harold will write the same letter except he can say with greater confidence I am writing on behalf of the National Bioethics Advisory Commission. But now it has been a month and a half.

But the second issue is I agree a more complicated one and how to approach that, how to get started on that topic.

DR. CHILDRESS: Okay, let's deal with the first one. Any further discussion of the first one, that is, making the request to see whether the information can be provided?

DR. EMANUEL: Gary is there.

PROF. CAPRON: I think we want to give him a chance and the FDA a chance to give us a formal response even if it ended up being a brief letter saying no, nothing has changed, just get it on the record and not burden him to enter into the discussion right now.

DR. CHILDRESS: Okay, again there is something that could have been handled just to the chair but since it has been raised, we will take it. Alex has made a motion along those lines. Is there a second?

DR. EMANUEL: I just want to clarify one thing. That request is likely to get us a numerator at best and not a denominator.

PROF. CAPRON: I am not asking for the data now. I am

saying there were observations made in these reports. To what extent has the landscape changed so that those observations are not just as valid today as they were 16 years ago. I mean, you know, the request was made for a change in practice. The change we know hasn't happened. I would love the explanation for why it hasn't happened but if there have been changes, I don't want us to look foolish by saying here is a problem and they say, there wasn't a problem. Don't you know? It has changed. Just get our facts straight.

PROF. CAPRON: I am not sure it is critically divisive issue but Harold is seconding the motion. Any further discussion?

DR. SHAPIRO: I will also write the letter.

PROF. CAPRON: All right. All those in favor of the motion indicate by saying aye. (Chorus of ayes) Opposed? (No response) Okay, abstain? I have one abstention.

DR. DUMAS: I don't understand the issue but that is my problem.

PROF. CAPRON: The second recommendation was that we find means, and I suggested a couple of papers, David suggested a third paper, as stimuli for our discussion and I agree with Zeke. In the end it is mostly our discussing that, I mean, we have to address the issue. It is a policy question but it would perhaps be helpful to have a couple of people who would take somewhat different views as to whether or not this is a good

idea or a feasible idea to establish such a government-wide oversight. I would differ with David as to whether or not that makes more dramatic a difference between federally funded and not but that could be one question that the person who writes the third paper could address. Or any of those three papers.

DR. SHAPIRO: I think this is clearly an interesting proposition and I think it is something well worthy of our attention. The only proviso I have is that we are going to be in the process over the next weeks of generating a number of ideas for these studies and I just don't know where this will get scheduled in. That is what I am not sure about. That just means whether it is done in the next three months or next eight months. That is what I am not sure of and a lot of people aren't doing it.

DR. CHILDRESS: I guess one thought was these would not be so much studies as really thought argument papers, pro and con from people who are familiar with the issues so it wouldn't require the kind of work or it wouldn't be, they wouldn't be as extensive as many of the other things.

PROF. CAPRON: We are thinking of maybe a five or ten page position paper more or less arguing it would be a good idea, it would be a bad idea, it would be a good idea if it were public-private as opposed to just --

DR. SHAPIRO: I think it would be interesting because it is quite easy to imagine good arguments on both sides.

PROF. CAPRON: I think we should hear those arguments.

DR. COX: The private part is really short. I mean, if you basically talk to the people in the department, they think it is a bad idea, we wouldn't even write a paper about it. That gives you an answer real fast.

DR. SHAPIRO: I am not sure which answer that gives. If any of you have any suggestions, not right now but as we think about it as to who are people who have thought about this. I will, of course, speak to Gary and others about any suggestions they might have but if there is any suggestions, please let me know so we can look at it.

DR. CHILDRESS: Is there general agreement that getting these two papers --

PROF. CAPRON: Three.

DR. CHILDRESS: Three papers would be appropriate and important? Any opposition? Okay, Alex, anything else you want to add?

PROF. CAPRON: No.

DR. BRITO: I don't have opposition but I just have a question that in terms of our budget, I know it is not limitless but when we are prioritizing what we are going to be spending the budget money on, --

DR. SHAPIRO: That is exactly why I said I wasn't sure if it was going to be done in the next few months or next eight months because this has to be, compared to the other projects

and it will get put in the line somewhere. I don't know exactly where.

DR. BRITO: Okay.

DR. SHAPIRO: This is not something that is going to cost so much money that you couldn't do it.

DR. BRITO: No, no, I just referenced this in general.

DR. SHAPIRO: It may not come quickly, it depends on how our priorities line up. You will have to prioritize these things. Our first priority right now is to get the work underway with the human subjects report done and the same thing with genetics, genetic information, something we talked about yesterday so that will be the first call on our resources and our efforts but then we have to start building an agenda which we will start to do over the next three to four months for something that follows on after January and February when these things come to completion so this will be in that linen but these particular studies are modest enough so certainly we can do them.

DR. CHILDRESS: Before we return to our plan on cognitively impaired subjects, David Cox wants to briefly make some comments about two items that were made available today.

DR. COX: Henrietta passed out, I brought back, I am the emissary from the President's remarks and the Health and Human Services remarks yesterday at the White House with respect to genetics and the insurance industry. I brought back two

things, one because they asked me to do it which was Francis Collins's comments which you may do with what you want and the other is the actual commission report -- that is said non-pejoratively, really, do with it what you want. The other is a report that Secretary Shalala handed to the President in the East Room and was the basis of his remarks so what were his remarks in sort of like three sentences and you can read because it is stated in that report that you all have.

DR. DUMAS: What report?

DR. COX: Health insurance. The purpose of the conference was, because the President has a new piece of legislation put together that he sent to Congress and is supporting. It was modeled after Congresswoman's Slaughter's bill, the same as Senator Snow's bill. The news yesterday that now Senator Frisk on the Republican side is supporting this also so you have the administration, you have 135 individuals in Congress behind Congresswoman Slaughter and you have Senator Frisk but what is the nature of this legislation and the purpose of it?

The purpose is to extend protections as far as the Kennedy Kassenbaum bill and to plug perceived loopholes there. The loopholes were in three major areas as outlined in the report to you. The first is, and this is protections for individuals who are not ill with disease but may be perceived to be at risk of genetic disease because of genetic tests and

because of risks to their family members. And so it has three key loopholes that they are trying to deal with, that is the insurers, and that is not just insurance companies, that is HMOs, anybody that basically provides medical care to people essentially cannot use genetic information to determine whether those people can get care or not and that is in terms of providing them the policy, in terms of canceling their policy, it is in terms of figuring out the charges on the policy and it doesn't affect if you have the disease in your family, if you have someone in your immediate family but it means that someone can't ask you or demand for you to get a genetic test outside of your family like some cousin or something like that to find out about that.

Furthermore, they can't change the cost of it so that is dealing with sort of with mixed use of the information. They can't, at the beginning they can't access it, they can't misuse it because they can't deal with the cost and they can't disseminate it so for instance that information can't be put into the general computer file of all insurance companies so everybody can look at this.

Now, you can read it probably more clear as it is written down there but the implications of this I think for the commission are quite striking. First is that it definitely carves off genetic discrimination as a separate type of discrimination from just medical stuff in general. I was

personally concerned about this a little bit but it deals with the specific issue that was very pointedly brought out by Mary Jo Alice Kahn who spoke and basically said my family will not participate in research because we are too scared but yet we desperately need the research and so that is I think the reason why the President is backing this as a separate thing.

So in that sense, the second point it is likely to get passed so with it likely to get passed, then there really will be a federal law on the books that basically says you cannot discriminate against generic information. Actually there is a third thing and please pay careful attention when you read it. It is the definition of genetic information so it is not just a DNA test but it is very broadly construed so it is in the context of your DNA, your medical record with respect to genetics, your family history with respect to genetics so none of that information will be accessible or be able to be distributed so I think ---

DR. CHILDRESS: Thank you very much and this will be sent out to the members who are not here.

DR. MIIKE: Does this supersede state laws?

DR. COX: It will supersede state laws, yes. This is a real problem. You read in this, it talks about the pluses and minuses of all of these different issues. Some states have much broader definitions of genetic information so actually you know, Larry, the important thing here is that this was just drafted.

It is a modification of the Slaughter bill. I can't tell you because I haven't read it specifically what it is so I don't know for a fact that it supersedes state laws so I would encourage, actually, Henrietta, probably for us if we could get a copy of what the proposed legislation is which I have never seen, that would probably be a smart move.

DR. CHILDRESS: Thank you very much for sharing that with us. I want to take five minutes on a matter that came up today and I would have built in more time had I known in advance but we have a tight schedule. Jim Shelton of USAID has been in conversation with the staff working on the federal agency report about some of the suggestions and thoughts for NBAC as a whole and circulated a single sheet, actually it is front and back or two pages on the, that lists some of his thoughts and we are going to take just five minutes at this point for him to introduce some of his concerns and not only his concerns but concerns shared by a colleague that we will need to keep in mind as we are working on the drafts of the federal agency report.

But furthermore this is to start a process of further discussion that will hopefully involve subcommittee members in the conversation. This you should have just received a moment ago. Henrietta passed it around to everyone moments ago.

PROF. CAPRON: We are sitting here in the Bermuda Triangle of distribution.

MS. HYATT-KNORR: I have some spare copies. Just a

second.

DR. CHILDRESS: Just go ahead since the clock is running.

**Agenda Item: Projects and Priorities**

MR. SHELTON: I didn't actually intend to have it distributed but I suppose it is just as well, at least when I came. I am the person for human subject research and I have been for actually about 20 years but also I am part of a working group from the interagency human subjects research subcommittee and I recently had a meeting really to discuss the common rule and a number of other agencies are interested in sort of engaging the common rule if you will although it might be sort of thinking the unthinkable in a way.

But the reason for trying to discuss this with you is because I do think it would be useful to have some constructive engagement, not just on this issue but other issues. We had the discussion a while ago about what happened if you have a party and nobody comes if the agency is not interested. I do think there is something to be said for some kind of engagement process so that is one of the reasons I am talking.

I have been a little frustrated, though, because I have heard a little bit of talk about how the common rule has been implemented but not a lot about the common rule itself although I heard reflections of peoples' opinions that made me think maybe they think there are some issues with the common

rule. My own view of the common rule is I think it actually worked very well but I also think that it has been 20 years and it has been largely unchanged in the last 20 years even though it has just recently been implemented in a sense. It had all this sort of incubation period and I think it behooves us to look at it again. I think there are some significant issues.

One of the lenses which I suggest people look at is one of the lenses I use which is the lens of the national performance review which is that we are trying to come up with a government that works better and costs less and when I look at the implementation of the common rule, and I admit I only got one view of that, I see a lot of effort that I see as relatively low yield and at the same time I think there is probably not enough time spent on more important things so I do think that there ought to be a way to try to deal with some of this.

Some of you may be familiar with this article that was in JAMA I guess last November or something called Institutional Review Boards Under Stress, Will They Explode or Change? I think everybody has seen it. I do think this is one person's kind of view of it but I do think it reflects a significant issue that many of you are aware of but I think it is part of the issue. I think there also are some other more fundamental issues of the common rule and I think we ought to rethink a lot of fundamental parts of the common rule and try to get outside the box even though the main framework I think is excellent.

I think the definition of research is actually a major problem and probably nobody even looks at that. I don't know. But as I read the definition of research, not only does it apply to this proceeding, it could apply to what the Supreme Court does, it could apply to the Whitewater proceedings, it could apply to what journalists do or even an extreme kind of what English literature authors do and not only can it reflect those things, it can reflect, it can encompass a whole lot of things in between and I think that is part of the data collection problem quite frankly is that not everybody knows what actually it is that the data should be collected on so one suggestion I would make is if you are going to collect data, try to be a lot more precise about then the rule is.

Dr. Emanuel, you mentioned at the end of each grant application process, blah, blah, blah, that is only one part of the way research is conducted in the Federal Government and there is lots of other research that does not go through that process at all, depending, of course, on how you define it.

Another major issue is kind of the one that Dr. Capron alluded to this morning about behavioral research. Behavioral research folks don't necessarily like the common rule and I guess I would suggest that maybe there is a reason for that. Maybe there is a good reason for that. Maybe the reason is that the biomedical paradigm that basically originated in biomedical orientation at NIH and so forth doesn't fit very well with

behavioral research and that is especially true not just when talking about experimental behavioral research, we are talking about surveys and anthropology, epidemiology and mystery plant surveys and focus groups and even evaluation. A lot of these things just don't fit very well in the biomedical paradigm.

I do think that one of the things that one ought to consider is to try to think of a different way of addressing behavioral research or different kinds of research.

So anyway I think that was basically, those are just two of the things I am concerned about. There are a whole host of procedural things in the common rule that I think could be expedited but again that is just my opinion and I think what we need is to have some kind of process where we can have a good dialogue amongst ourselves in the federal agencies but also engaging you and other folks to try and figure out ways to streamline procedures on the one hand where they need to be but strengthen them in other ways where they need to be as well.

DR. CHILDRESS: Thank you very much and we will offer just a couple of questions. We are and have been from the beginning interested in looking at the common rule and not simply how the common rule is applied or how well agencies have gone beyond the common rule, even what we are doing with the cognitively impaired subjects is an attempt to see whether the common rule needs to be redone in relation to that group.

Similarly when we talk about whether we are going to

do something in the area of children and adolescents, whether to look at that again and obviously a concern to us would be precisely the broad conceptual questions that you have raised and I think it is very important that you came forward and have indicated a way in which we might think about a process of interaction discussion between NBAC and the agency representatives most concerned with this so we would like to pursue those possibilities.

Let's just see if there are any, a couple of quick comments or responses, questions.

PROF. CAPRON: I have a quick one. Do you participate as your agency's representative on the interagency committee? These must be issues you have raised there. Has there been any response?

MR. SHELTON: Well, not everybody agrees with me which is a good thing but the response of several agencies at the last meeting where I sort of raised these issues and we actually had an excellent discussion. The agencies then said they were interested in specifically working on this working group where in addition to AID and OPRR, working on it, DOD, CDC, NSF, Energy and NASA so there are some other agencies that definitely see that there are some issues here.

DR. CHILDRESS: What is your timeline for your working group?

MR. SHELTON: I don't know.

DR. CHILDRESS: Let's explore after this meeting some possibilities and we will try to set up some modes of interaction. We will let the commissioners know and see how many might be able to join us for some of the conversation. Two last comments.

DR. SCOTT-JONES: I just want to make a comment that we need to be very careful when we compare biomedical research to behavioral research. Harold had mentioned earlier that we need to think about the differences and I just want to encourage us to think about them really carefully and some of the comments that are here, I wish we had more time to talk about them. Some of them bother me just a little bit and some of them are the same kinds of criticisms that have been made of those of us who are now revising the standards for the American Psychological Association and the American Psychological Society, our principles for research with human participants.

Your last bullet in your first set that there is a double standard for applying ethical conduct to research as opposed to non-research activities, one of the comments that was made was that invasion of privacy happens all the time to persons, for example, police officers are allowed to invade the privacy of persons. It is sort of why can't researchers do that but all these comparisons are a little bit off the mark when you think of what behavioral researchers do and we do gather a lot of information about people that could be used in ways that are

damaging to those persons so there are a lot of issues that really should not be taken lightly. Behavioral research even though it might be in the form of a survey or a face-to-face interview or a focus group, has lots of issues related to it and I would really not want us to just wave them away lightly and say that because it is not biomedical research that is doesn't pose any risk to the persons who participate.

MR. SHELTON: Can I respond to that? I think it is pretty clear that two wrongs don't make a right. I mean, that is basically the kindergarten lesson that I would apply to the situation but I think you could also take your concept and apply it. The other way to apply that is we should be trying to apply ethical standards to lots of things we do, not just research. It doesn't mean we don't apply ethical standards only to research. I think we need to apply ethical standards to a lot of other conduct.

My concern about behavioral research is I am not saying don't have rules. I just think it needs to be looked at a different way. I think, for example, the informed consent requirements, what are my alternatives, I won't lose benefits, who do I call, et cetera, et cetera, makes sense in some behavioral research but they don't make sense in a lot of survey research. Now, they can be waived but to waive them requires a sort of wading through a fairly intricate maze to do that.

DR. CHILDRESS: That is part of a conversation we will

need to have.

DR. MIIKE: I think that just all of today's discussion starting with Bill Freeman's presentation about the, just all of today's discussions ranging from the very first presentation by Bill Freeman and staff on the survey just sort of points to the fact that the common rule, just by name itself says that it is a one size fits all kind of situation and I guess my concern is that it hits you on both extremes. One is that it hits areas that may not be appropriate for so people just go through the motions and it hits other areas that it is very appropriate for because it is so broadly over-reaching that they don't really get the precise kinds of things that you should be putting under there but I think all the discussion we have had today, no matter who the speaker was talked about being a little bit more precise in application of the regulation, whatever kind of regulatory structure to the activity at hand.

That has been going on all day long today so I think we are well aware of that, the question becomes if you are talking about a sort of a process, whether we vulcanize it to the point that we have no longer a system, then the application of oversight is in the discussion.

DR. CHILDRESS: Well, thank you very much. And we look forward to carrying on our conversation. Let's pick up our discussion of decision impaired or cognitively impaired research subjects. Let me just bring together some things and let's talk

about then how we might want to proceed.

We have had at different meetings, as I mentioned this morning, testimony from a variety of people involved ranging from ethicists and lawyers to researchers and we have had a superb contract prepared by Rebecca Dresser. We have Jonathan Moreno on staff now to help us prepare something in this area. There are some things that could already be done in terms of the report. Background, history, all the discussion of what happened to the proposals regarding those institutionalized as mentally infirm, that whole debate over a period of years is a very important part of the background.

We have, building on Rebecca Dresser's work and Jonathan Moreno' work a possibility of beginning to write a kind of framework of analysis from an ethical and legal and policy standpoint so we have those themes.

What else do we need? We certainly need to hear from patients, subjects, families and representatives organizations than we have. That is critical. We have talked about the possibility of doing that at our September meeting. I was also informed by Rebecca Dresser over the break that the New York commission is planning a series of some public hearings as well. So it may be possible to coordinate and take advantage of these what is already underway though it is not clear when that will occur.

Second, we need clearly to have some time as a subcommittee and

as a commission so to have a framework of analysis and the issues well laid out, we don't know where we are on the whole range of factors and we need a half a day at least just to sit down and begin to sort that out. Now, Jonathan, on board, can help sketch some of the options in relation to Rebecca's paper in very short form and perhaps at part of the September meeting we could do that as well. That would certainly be a possibility.

There are also suggestions that have been made for hearing from a few researchers who do other kinds of research, not a large number but a couple of others and then there is the NIMH consensus conference that is being planned and obviously that is something we want to be closely related to in our own work.

Those are some of the things that are in place, being planned and the like. Now, the question is do you feel comfortable in proceeding along those lines of trying to do background analytic work, conducting public hearings either separately or in conjunction with the New York commission and trying to set aside some time which we can really reflect ourselves. We know some positions, we know Trisha's position, our advanced directives and so forth but we really don't know where we stand as a group. What are your thoughts?

DR. MIIKE: Do we have a deadline?

DR. CHILDRESS: We don't have a deadline. We were

shooting for the end of the year.

DR. MIIKE: All right. I get a little concerned when we begin, our deadline begins to get influenced by what other groups are doing and the interrelationship. It will never end if we do it that way so it would be nice to consider and I know NIMH said we would reconsider the consensus development conference but I think we should not be swayed too much by what other people are doing. Also it depends on what exactly are we going to be producing in terms of a report. We can get very specific or we can sort of charter a pathway for us and others to follow and make sure we follow.

DR. CHILDRESS: I think that is an important point for us to reflect on, what level of generality and specificity do we think would be possible in our report. Now, some of that essentially, now I could be wrong on this, it seems to me that, and I could be wrong on this but it seems to me that we might think in terms of the background and bring what analysis, whatever level we end up in terms of degree of specificity or generality. We might conclude by saying, well, given our reflections on the analysis that has been presented, all the things we dealt with, we feel comfortable in offering the following kinds of guidelines and give them some of the things we heard this morning.

For instance, there may be an argument that it is premature to move in the direction of very specific

recommendations but that is something it seems to me we probably won't be able, perhaps we are not going to determine until we go through that hard reflection ourselves.

DR. CASSELL: I think from this, from what we have heard today, from our questions back and forth, we may be going to really move away in dealing with the issue, the issues that were presented and I would hate to see us foreclose that possibility by trying to have a fix or earlier fix as to some of the problems. I like the idea of that paper that would give us meat to discuss and also let our thinking be known to the other people also so that we can begin to go towards large understandings of the process of participation in research.

DR. DUMAS: I think a general plan sounds good to me. One of the things I feel a need for is the opportunity to come to some consensus on what critical issues we are trying to address to define the issues. And one for me has to do with terminology. As I mentioned earlier, I don't like the idea of settling for the rubric of cognitively impaired subjects or decisionally impaired and I would make, as I said, the recommendation that we use a broader term.

My preference at this particular moment would be to use

something like questionable decision capacity because we don't have sharp mechanisms for really diagnosing decision making capacity I would suggest. So we need time to come to some

common agreement about what we consider to be the critical issues and then the method of, for addressing them to me it becomes a little bit clearer.

DR. CHILDRESS: Thanks.

DR. EMANUEL: I think Harold is first.

DR. SHAPIRO: I just have a suggestion and a comment. The suggestion is that we have meetings on the 18th and 19th that are currently scheduled. It seems to me that a useful thing to do might be to have each subcommittee meet the morning of the 18th and you can carry on whatever discussions you think are appropriate to clarify your own thinking on issues given whatever reports will be available at that time. The entire commission can meet in the afternoon here, what the subcommittees have to say, review the discussion.

We could then go to public kind of hearings that we would like to have the following morning, reserving the following afternoon for whatever else you think is appropriate. That is just a possible way of thinking what we might do in September. But regarding this deadline, it is true we don't have a deadline. That is, there is no one out there who is waiving the 90-day deadline or something of that nature but I think it is very useful for us to have a deadline, to mobilize our own thinking and to force us to get down to it because there is always something else to think about and I think it is important to remember that this human subjects area, we have one

very important and ongoing activity that Bill Freeman and his colleagues talked about this morning.

We will have very substantial reports by the middle of August, phase one and possibly phase two both by September. I think that is what you said, and it seems to me that we will have quite a bit to say on that issue and that is we are saying as soon as we feel comfortable. Now, I can't predict whether we are going to feel comfortable in September when we review this but I think adopting an objective on that issue that we ought to really have a report this calendar year. We will probably meet again in October and November and I don't see myself any reason for us not to have a very substantial report on that aspect.

DR. CHILDRESS: We were actually shooting for the end of October.

DR. SHAPIRO: And so I think we should think of that as

our deadline although we are reserving the right, if we are not comfortable, to of course change it.

Now, the second issue, the second big issue which the human subject committee is currently dealing with as I understand it, Jim, is the issue, whatever term we used, decisionally impaired, vulnerable, various other terms that have been offered here today, on that issue. This, unfortunately, is not a new issue as Al is going to testify perhaps better than most of us here and I feel some urgency at being able to get our

thoughts together, not to be able to solve every last issue that is here because we can't do that but identify a series of issues which we think need some attention now and the way I would propose we get to that, Jim, I think it is really just repeating what Jim said yesterday.

Sometimes in the September-October framework, identify those issues that we feel we can deal with now and perhaps try to deal, effect what we might have to say on that issue also within this calendar year. That is a lot, I mean, we are on that certain ground here, depends on how this discussion works out, whether we agree with each other or don't, there is a lot of uncertainties there but I think if we in general have in our head the kind of schedule Jim talked about, I think it was yesterday, the days kind of merge together in my head, but I think it was yesterday which would give us something to say on both of these issues by the end of this calendar year is something we should strive for, leaving open the possibility that maybe we can't make it, maybe there will be some very good, persuasive reason to lay one of the other of these but I think it would be helpful if we took it not quite as a deadline but as something we would like to get done, give ourselves some discipline and focus.

That is just a suggestion, Jim, it would be up to the committee to decide whether you can make that or not.

DR. CHILDRESS: We have got a couple of other comments

and then come back to the question as to whether parts can be presented as how we would like to spend the time in September. I have Zeke and Alex and Trish.

DR. EMANUEL: I want to apologize. I am going to run unfortunately right after my comment and not because I don't value what everyone else is saying. I want to separate out and just focus in on the decisionally impaired report and it seems to me that until one has a substitute discussion and we really know how much disagreement and how extensive substantively we want the report to be, whether we want to really, as has been just suggested, reconsider some substantive aspects of the common rule, suggest major changes there or not with this group, it is hard to know what kind of timeline you can have.

If it is going to be more focused report, if we find a lot of consensus on certain aspects, then the end of the year seems reasonable. On the other hand, my own personal feeling and again not from any deep analysis of the issue, I am by no means an expert on it, suggest that it is a bigger issue than that. There are so many groups dealing and confronting it that if we really want to have an important comment on it that is going to be taken seriously, it is going to have to be broader ranging. Just the definition as Rebecca Dressel reminded us of what is going to come into this category, it is going to be highly contentious, going to take, it is going to be very difficult to write it seems to me. Then to talk about the kind

of ethical outcome we would want and then the kind of procedures we would want, I think it is more reasonable to try Kyle Murray's approach which is to walk backwards.

How fast do you have to run to get to that deadline and

it seems to me that if we have a report on federal compliance with the common rule this year, and then maybe mid-March or something for a report on the decisionally incapacitated or whatever, bearing in mind that that data will have to change depending upon our real substantive discussion and I would suggest we probably, again, I am not a part of that subcommittee but the sooner we have that discussion, the clearer it is going to be how fast or how far we can move.

DR. CHILDRESS: I have it in September. That would be the goal but the subcommittee has actually dealt with this at each of its meetings so it is not as though today is the first day, and given the other things in the way, including the consensus conference, it seems to me that at least to think about the end of the year rather than March is not impossible. Again, a lot depends on what happens in September when we get together.

DR. EMANUEL: Let me just make one other observation and this is sort of general, actually based upon my discussion. I have been reading the transcripts of what has happened and most of the material but not being involved in all the

subcommittee hearings. I think the consequences, the rest of the commissioners who aren't there at the subcommittee hearings, it takes time for us to catch up to speed, even if we are fairly conscientious about reading that. A lot of the discussion we had yesterday about the framework we had for the genetic was exactly the reverse. Those people who are on the subcommittee of informed consent needed some time to hash through exactly the same issues we had at our previous meeting in March.
I think that also slows down the process but I think it is important for all the commissioners to feel comfortable with the recommendations that are going to go forward under our joint names so that is a bit of a trade off with the subcommittee arrangement but it is also something to be aware of when we actually get to X.

DR. CHILDRESS: Your point is well taken. Alex?

PROF. CAPRON: I think I am largely in agreement with the departing Emanuel here and I guess my sense of what schedule makes sense is in part dependent upon what kind of staff we have to work on this. We have got a couple days a week from Jonathan and at least one of those is now going to be devoted to working on the federal compliance report which I agree we have got to get out in October if possible, shortly thereafter and certainly this year and that is a particular requirement we have from the President and to me it is only skimming the surface. I mean, it is going to be a very good and valuable report but it doesn't

get to that third level of application that always worries me.

So it is necessary to get that done so maybe we can move onto the other. I don't, can we learn something about what kind of professionally qualified people of the type Dr. Moreno are going to be on staff? Do we have any sense of once we have an executive director, how many people we are going to be able to have for this?

DR. SHAPIRO: I think we have, from the point of view of bringing on staff to aid in the commission's deliberations, the subcommittee's deliberations, we have substantial capacity. I don't know how to answer the numbers but we have substantial capacity if commission members or committee members can identify people, we have substantial capacity for extra.

PROF. CAPRON: Because what I think we need, and I take this from Rheataugh's comment earlier, we need to have a draft of a paper, not a paper, excuse me, but something quite substantial in front of us that we begin to look at as our work. That is to say, it comes from our staff rather than a consultant giving us good advice and only that in my experience will begin to provoke the focused discussion that will lead us towards agreement or if there is disagreement, Mr. Chairman, at least clear lines on what that disagreement is. If it is not bridgeable, there is no reason to bridge it, it is a state one position and then the alternative and some support one and some support the other.

DR. CHILDRESS: I agree with you completely and

actually that is what I was proposing. That Jonathan do that in relation to Rebecca Dresser's paper. You got a copy of Rebecca's paper, right?

DR. SHAPIRO: Yes.

DR. CHILDRESS: I think that provides 75 pages of superb analysis but you are right, it is not worked in the from the standpoint of what we might, that is what Jonathan will be doing.

DR. SHAPIRO: And even within that, the kind of point that Rheataugh was talking about was only in questioning to Rebecca about which term would you use and you really said to her, you use this and you use that and she said, well, I thought I would focus on it. But what groups are we talking about and we heard so many different views about whether they, whether lumping or splitting makes more sense here and even if we are concerned about decisional capacity, is that the way to describe the category or not? I mean, those are all substantive issues we have got to debate.

One further note because I think we have begun to get onto the 1:30 time period stuff as well because we are talking about many things. My own view is that the report that comes out this year might be able to deal with at least one additional issue, mainly the compensation for indigent subjects in research. If it turns out that there isn't a lot of new work to be done on that, it is really a matter of coming back to

conclusions that have been reached in saying the time has come, let's do something about that and the commission wants to see something done so that I wouldn't see that this year's report as only addressing the compliance issue. It could have most of it on that and then other topics the commission is addressing.

What that could do is provide us with a little breathing space if, as Zeke predicted, it turns out that some of these topics won't be done by the end of this year on the decisionally impaired and I would rather see us then say well, aim for a date in 1998 and really do a very substantial, complete treatment and to answer Larry's point, I think I am agreeing with you here, Jim, I am not clear what levels our recommendations will be. It in part depends on how far our thinking can carry us. On some of these we may say we have reached the definite conclusion, just throw out an idea that we talked about this morning and just not debate it, we reached the conclusion there should be a separation between the role of investigator and treating doctor and that there should be some evaluation function, however that is carried out, independent of the investigator up to the capacity of the subject to participate in research.

That is a very concrete, specific recommendation that if agreed to would be reflected in federal regulations. We might, on another topic, like advanced directives, talk about the uses and advantages of those without saying that they would

have to be placed into regulations. We might, in fact, be offering this as a tool to institutions or to states if they want to adopt it, if Maryland is going to. In other words, we might have different levels of recommendation depending upon the topic we are talking about.

I don't see us having to do the same thing as to all.

DR. CHILDRESS: Good point. It seems to me that I guess one question is whether we need in effect to set a deadline, I mean, whether we need to postpone it until February or actually wait and see where we are in September but if some of the work is going ahead anyhow there will be a kind of foundational kind of work for us. We need to do the public hearings, that is, we need to do these sorts of things. I don't know that we need at this point to set a firm date.
But if we do set it later than obviously that would have a bearing on when the National Institute of Mental Health sets it consensus conference. They were planning a little later than would have been appropriate were we shooting for the end of the year.

PROF. CAPRON: I have a sense that there will be, after than consensus conference and after a lot of input, we will need a number of sessions looking at drafts and refinements of drafts and having substantive discussions as commissioners before we are comfortable. When you think of the amount of work we did on that cloning report, it was a brief period of time but

we were meeting all the time and a heavy duty exchange of drafts and everything. I don't think we can do that again and I frankly don't think it is appropriate for the commissioners to be doing the writing because I think, the principal writing, because I think that distorts the discussion process to a certain extent.

PROF. BACKLAR: I have a number of points and I will try and make them as short as possible. One is I do think it is terribly important as you have suggested that we have a meeting, our next meeting we hear the other people that we didn't hear today, consumers, families and also researchers who work in imaging.

I do feel that there is a lot of unfinished business from the discussion today. We heard an enormous amount this morning. It was very compact and we need to have time to explore what we heard today and what we will hear hopefully with these groups of people who will come to us next time. So it seems to me that it is a shame that we can't have a full day. What would be really wonderful is today would be to listen to everybody this morning and then discuss this because there are things that everybody said which are extremely interesting and important that we would want to discuss amongst ourselves. I am thinking particularly, for instance, and I don't mean to diminish anybody else's contribution today, but I am thinking of Dr. Appelbaum's slight discussion on the issues of agreement of

criteria for capacity which is something that went whipping by that we had no time to address so that is one point.

The other aspect of this is I am concerned about our scheduling inasmuch that if we have the committees overlap, one of us has now become obligated to two subcommittees and I know that one doesn't reorganize their whole schedule because of one person but I think there is something we have to discuss here. Perhaps privately but I also felt, other than my individual interest in listening to both committees, I thought it was a great benefit today and yesterday to have many members of the subcommittee as audience and participating somewhat and if we are going to have to write off on each of these things it may be an important way of doing it. It may be exceedingly inefficient. I understand that.

DR. CHILDRESS: Diane and then David.

DR. SCOTT-JONES: I want to say that I agree with Trish in her statement that it was good for us to be part of both subcommittees because a lot of what was talked about in the genetic subcommittee really had to do with informed consent, community consent and so forth so I don't know how we can work that out to stay more informed about what each other is doing. The comment that I wanted to make as far as our planning and what we do to come to some conclusions about research participants whose capacity to make decisions is questionable. Is that okay, Rheataugh? Research participants whose capacity

to make decisions is questionable.

That we might want to consider what we would want to do, what, if anything we would want to do on research with children and adolescents because both in Rebecca Dresser's paper and in a lot of the discussions analogies were drawn between persons whose capacity is questionable and children who, because of their developmental status and their legal status don't make decisions for themselves regarding participation and we also have the writings from the Society for Adolescent Medicine wanting us to endorse their recommendations for guidelines for adolescents. So because some of the issues are similar, we might want to consider that as well or at least have some sort of bridging of the one topic to the other and I know you were going to say a little bit about that at a later time.

DR. CHILDRESS: One of the major differences, of course, is we do have regulations in place for children and they do serve as an important point of reference for much of the discussion in this area. David and then Rhetaugh.

DR. COX: A couple of points. First, this issue about both groups primarily on the genetics but I completely agree that these things go back and forth so I think that the way you do that is you come to each other's meetings. You can’t be at both of them. Not everybody on the genetics is so interested in all of these areas but if we have a few people going back and forth we will be in good shape.

PROF. CAPRON: You can't mete out their schedule at the same time.

DR. COX: That is not true.

PROF. CAPRON: Is this advances in cloning?

DR. COX: They obviously can't come to the entire meeting so I am not recommending that they always be scheduled back to back but I think that even if they are scheduled back to back --

PROF. CAPRON: It is not back to back, it is simultaneously.

DR. COX: But the point is everyone can't do that. But I don't think everyone wants to because people have picked one or the other for that purpose. I am just saying that the more we have people, in fact, in some of these situations certain processes they have people that are called bumble bees. That is what they do. They are not on any particular one and they go from one to the other while they are meeting simultaneously and they do the same thing, the bumble bees do, which basically cross-pollinate what is going on.

So I think it is not, but I like the idea of cross-pollination, that me being a cross-pollinator in a sense here, I would just like to reflect what from me I have learned today and the punchline is I am very much in favor of some, I think what I heard or took to be Eric's suggestion.

I heard today that we are talking, although we may

have started talking about people that are, may more or less be able to make informed decisions is that everybody when they are ill is at some deficit in that regard so this is a matter of gradation, not a matter of it being really sharp.

We have all these different groups of individuals, whether they be children or whether they be people that are psychiatric disorders or whatever but it is all an issue of informed consent and if it is the issue of informed consent of the people who are, quote, subjects, understanding, so that is what a lot of it has been. But then it is an issue of informed consent, the people who are the researchers trying to get people to understand. And lot of the focus has been on the subjects, can they understand or not but we had a lot of testimony and discussions about the researchers, how are they getting the people to understand.

And so I think you can do it very broadly in terms of the issue of an informed consent with those two areas and subsume a lot of these different subgroups. If people are willing to be brought, now I really like this very broad stuff in the context of ultimately specific suggestions so it is practical but that is just a cut that I take on listening to this today for what it is worth.

DR. DUMAS: I had, when I heard Harold talk about the schedule for the 18th and 19th, I assumed that each morning a different subgroup would meet and each afternoon the entire

commission would meet and then we would have public comment. So I would like to suggest that as a format, that on the morning of the 18th one subcommittee meets, then the full commission that day and the next day the other subcommittee meets in the morning and then the full commission and this gives us all an opportunity to participate in the discussion. I think it is time now that we did that because issues are cross-cutting.

PROF. CAPRON: Let me ask Rhetaugh if what you are suggesting is in effect that the morning would be devoted to one of the two topics. At that point it would, we really are not, and actually I endorse the idea entirely but I don't think we should be talking then about those being subcommittees. That really is the whole commission addressing that topic.

DR. DUMAS: I think, what I am suggesting is --

PROF. CAPRON: We might have some person who might not come to the commission meeting, people don't come now who are members of the subgroup sometimes.

DR. DUMAS: We might want to change it and I might change my mind but what I was suggesting was that we not dissolve the subcommittees. That each morning one of the subcommittees would take the lead for the discussion as we have done in the past. And then in the afternoon it would be a common discussion of the entire commission on the topics that were presented that morning.

PROF. BACKLAR: This may be a benefit of our funding

experiments inasmuch as we have maybe begun to work together a little bit better.

PROF. CAPRON: If I may offer just one other observation. The President's commission which had 10 different topics that it worked on, didn't have any subcommittees, the whole commission work on all subjects and there was a period when the meetings were coming fairly frequently but I think that the advantage of the subcommittees is more or less the laboring o'er and making sure things are going to organized remains with the subcommittees but increasingly I think what we have heard here is there is so much more value of having the full commission be there because, as Zeke said, otherwise the commissioners who aren't there are going to, will say to everybody who was there, will you go over what happened this morning. If we are there, we can just go ahead with the discussion.

DR. DUMAS: You see, that is why I think we ought to do morning subcommittee, afternoon entire commission, morning subcommittee, entire commission. It is all right to do it as a committee of the whole until it comes to the time of deciding what is going to go into the report and getting certain parts of that report and having people who spend more time thinking about a particular aspect of it. That is why I think we should keep the subcommittees.

DR. MIIKE: I agree with that and we are really going

to have one topic one full day, another topic another full day because we are all going to be here whether we attend a subcommittee meeting or not.

DR. DUMAS: Well, yes. The prime focus, the major focus on the first day, say, would be on genetic issues subgroup and then the next day would be on the human subjects issues but since they are cross-cutting there is no prohibition of putting these ideas together as we discussed them.

DR. MIIKE: I am not arguing with you. I am just saying as a practical matter what we are having is one full day on one topic and one full day on another. The same people are gong to be here morning and afternoon.

DR. DUMAS: Absolutely, right.

DR. CHILDRESS: So the proficiency, one could in effect merge the subcommittee and the whole. It is not clear when we need to do both parts if it is going to be on the same topic and if all the people will be in town.

DR. DUMAS: The only value that I see of not merging the subcommittees is what are you going to do with what comes out of those discussions. If the staff is going to take them and put them together and decide on how it is going to go, but the subcommittees have brought us up to this particular point. There is some perspective on what we want to do, the objectives and that is the reason why I think the subcommittees should remain intact but no, I think the discussion should be across

the entire group.

DR. CHILDRESS: Harold, do you want to pursue this?

DR. SHAPIRO: The issue of whether subcommittees meet concurrently or not is not simply a matter of what is a good idea in principle, it is a matter of how much time the people are willing to give the commission and we are having enormous difficulty getting people to be here and therefore when you meet separately it just expands that difficulty so I have no problem in principle with all of us meeting all the time as a commission. It is just trying to really face the reality of how much time we can really get people here for which is a serious difficulty I can assure you so that I am quite happy to go ahead, assuming that we will meet as often as possible to get because for all the reasons that were said here, which makes sense, that seems like a good idea to me.

It also is true if we just take the suggestion Rheataugh just made, that is, fine, we can do that except it is inconsistent with another suggestion, namely that we spend almost half the day hearing from constituencies we haven't heard from, not just that we have a half hour for public comment. We spend a whole half a day on it so it is just trying to put these things together. I understand how peoples' sense of this and all I can say is let's meet as often as we can together but in order to move the work forward, sometimes it is going to be necessary for people to meet separately and I understand the

benefits, cost and benefits of all of this.

With respect to the model that we use, Tom said yesterday and I will repeat it today, he didn't think the model we used for generating the cloning report is sustainable long term where the commissioners took such a direct role in the writing itself. I think that is by and large correct but nor do I think that we should move to a totally different model which says that we will just judge what other people write because I really believe that there is more, certain kinds of qualities that commission members bring here which we are not going to be able to replace by the staff in my view. Now we will have to wait and see. As soon as it comes, see what happens, that is an open issue to be decided as we go along.

But for the commission members, I want to make sure you understand that I expect to be asking commission members at appropriate moments to continue to do some putting pen to paper even though the staff will take on the biggest share of the burden as we go along because I don't think we can sustain literally the cloning model all the way through and that is, of course, one of the very valuable reasons we have Mr. Moreno here now who will be such a help I am sure to all of us in this case and we are very fortunate to have him so we will go ahead with some mixed version here because just the practicalities of it forces us to mix these strategies.

But as far as the turning to the question which got us

started on this, how far can we get. Let's say this calendar year versus March or April or something. That is not my view of the big issue. We ought to learn as we go along it is not, we don't, as I said yesterday the plan I currently have for the report is we will issue at the end of this calendar year our sort of mandated report. It will be a report in and of itself just sort of detailing what we did during the year and so on and will not incorporate in that report itself either the federal agency evaluation or any other particular activity.

It will be descriptive of what we do and hopefully be an interesting document but still it will be just basically descriptive and we are already beginning to form the outline of that report and I will have an outline to present to the committee in September for your review and for your help and assistance in that but that will go ahead on its own independent of all these other issues.

PROF. CAPRON: You said calendar year. Is that not something that we have to turn at the end of the fiscal year?

DR. SHAPIRO: I am told that the actual deadline for delivery is December but that it right, it will deal with the activities of our first year and where we are going and what we are doing and so on so it will go sometime November, December, some time, but at least before the meeting so that will stand by itself. It is just the part we are mandated to give you. The other reports such as the issue of the federal agencies or

the vulnerable populations issue, that is a word we use as a shorthand, I think we will have to see where we are in September. We don't have to decide anything right now. My only focus is I am trying to keep a certain pace going here but we can't go faster than our wisdom will take us and we will just have to judge as we go along in December as to exactly where we are.

I am very confident that we can do I guess Jim has been calling it phase one and phase two of the what I will call the federal agency evaluation by this year and I think we shouldn't accept anything less than that because we have the data, we have people who have been working very hard on it and very effectively on it for quite some time. It is mandated in the executive order. We just ought to get on with it, recognizing we won't solve all the problems but we will solve quite a few, I believe, on the basis of the work that Henry and others have done on that.

Regarding the vulnerable populations issue, of course, that is a huge issue in one way and we will have to decide when it is that we think we have something to say. We may have it relatively sooner than we expect but maybe we have to wait and have it mature a little bit in our minds. So we don't have to go away from here today thinking that it has got to be December. No, it could be March. Let's just see where we can get by September, what the quality of that discussion is in September, to gather the quality of the material that we have available and

make the decision then.

If that seems sensible to people, we just go ahead on that basis. Now, Jim, I really want to rely on you and members of your crew to tell us just what you think we need regarding public testimony. Quite aside from those who may sign up for public comment, that, of course, is part of every meeting but what others do you think we might invite and how much time do you need is most important for that because we could do it both in oral form or in written form We have some options here.

DR. CHILDRESS: And this is something I am going to have to bring a lot of people in on, especially people who are closely involved, Trish and Laurie and others but this is something we will need also I think to make an announcement about in the appropriate publications or at least e-mail in order to make sure that all the people who might want to represent particular groups would know about this and be able to testify. So I don't, at this point, some groups, individuals who have been mentioned but I don't have --

DR. SHAPIRO: I don't mean right now.

DR. CHILDRESS: It is obviously something we have to turn to very quickly.

DR. SHAPIRO: What I would really like to do is issue invitations whether it is for written or personal testimony, I mean, personally presented testimony, either way, I would really like to be able to mail that out early in August to give people

a chance to put together whatever they want to put together and so is that unrealistic?

DR. CHILDRESS: No, I don't think it is unrealistic. Laurie?

MS. FLYNN: No.

PROF. BACKLAR: We have already discussed this actually.

DR. SHAPIRO: The sooner the better just so we give people sort of a genuine opportunity to get ready if they are interested and concerned about it.

DR. CHILDRESS: Okay. Is there any objection to Harold's proposal about how we treat the dealing, that is, not set it but we have set a process and then we will see where we are in September? That is a deadline on the cognitively impaired, decisionally impaired subjects. Is that agreeable with everyone?

DR. BRITO: What they are going to solve is the teleprompters we had, not discuss the subject matter necessarily but to outline where we are going because I think it, so maybe sometime in August we can do that.

DR. CHILDRESS: I will have some materials ready to circulate. Okay, anything else about cognitively impaired?

PROF. CAPRON: Not about cognitively impaired subjects. DR. CHILDRESS: Let's turn then to the question of compensation which has been raised. I would just note Alex

has brought this up already. It is something we have talked about, something we have considered to be a priority. Something we have considered to be doable and I mentioned that at one of the previous subcommittee meetings, so I will just direct everyone's attention to this as we look at the building public trust of the response of the President and Clinton administration generally to the issues raised by the advisory committee on human experiments.

The administration will be open to consider any recommendations from NBAC or legislation from Congress that seeks to address the issue of compensation for research related injuries so there is kind of a presentation there as well as a recommendation that in the absence of a fine, there is a significant number that are unfairly denied compensation. The administration is not prepared to propose a system outside the existing network of federal and state liability insurance systems.

We have also, and you received in your packet last week just a brief report from the University of Washington which for a number of years has provided compensation for research related injuries and I don't think we need to discuss that in depth today.

The person from the University of Washington who directs the Office of Risk Management would be glad to join us at some point. She insists that some of the keys to controlling costs, and you see the cost figures in the document include

having an excellent consent form so that the central subjects can self-identify contra-indications, a rigorous adherence to protocols, prompt reporting of adverse effects, and a willingness of the institution to provide services at no cost to injured subjects or the compensation plan. That is some of the ways that costs have been held down.

Alex, you proposed today that we could probably do something this year and I agree. One possibility would be since you and I have had a longstanding interest in this, would be perhaps to work with Jonathan to try to draft something if you would feel comfortable with that or we can get a contract paper.

PROF. CAPRON: Have you explored the contract paper that I suggested some months ago?

DR. CHILDRESS: I had talked to her and it sounds as though this is not an area that she has been following.

PROF. CAPRON: I think there is some need for some staff work on this. Obviously I agree with the chair that the commissioners are going to do some drafting. My concern was really not the time demands. I think that there is a problem with a very diverse commission, unlike the National Academy panel where everyone comes from the same sub-discipline and is pretty much started from the same place, having commissioners heavily identified with certain drafts I think just constrains other people the way having a staff who you have hired to do something, if they don't come up with what you want to tell

them, they have to come up with whatever you want.

I think there is a problem at some level with relying too much on it. With this particular topic, my sense was that the, I am sure you all get tired of hearing me make references to what the President's commission did. It is one of those topics with the President's commission, it is about the third, this is one where we were about the third of fourth group to address it and all the groups have come to basically to the same conclusion which was there needed to be some form of compensation.

The problem that everybody who made that recommendation ran into was the fear that this was, it is a double fear. One, that having such a system would greatly increase the number of reported injuries. That when you don't have a system and you make the announcement which is now part of the common rule requirement that you tell people you are not going to give them any compensation if you are not going to, and most institutions tell them exactly that, many institutions informally will take care of costs and some may even informally make payments of cash for inconvenience and so forth but they don't announce it up front and they are apparently able to do that and it is done very quietly but the sense was if they announce up front that they have a system that they would create a lot of spurious claims or claims that they wouldn't have to pay otherwise.

The second concern was the total amount that would

therefore be added to research budgets would be burdensome. We looked at a couple of examples, Washington was one of them, of systems that were already in place that didn't experience that kind of problem and said why not use them as examples. People said that is Washington, that is special or that is Iowa, whatever it was, that is special. That is the Scandinavians and they have health insurance so you can't generalize. Each of the examples was met with an argument.

So we made a very concrete recommendation addressed to that issue which is conduct an experiment. Act like scientists about this and set up a system on an experimental basis, not a new entitlement or something, just something that is going to be tried at a certain number of institutions, and see what happens. That was never acted on

We now have many more years of experience with the University of Washington. I can't fully interpret this report. It is in schematic form. It seems to say that they paid $4,110 in the last 18 years in claims. That does not seem very burdensome. Obviously that does not as far as I can tell, the cost of medical services and it would be interesting to know that. But then again many institutions either do say we will cover your immediate medical care or don't say it but in fact do it so that may not be as big a change.

I would, so I don't even know whether I would be satisfied simply repeating that recommendation and saying do it.

You know, we are serious about it. Mr. President, you asked for our recommendation. Our recommendation is do this. Congress, you wanted to know what to do? Give them some money to conduct this study.

Or whether we by now ought to be saying implement a program. I have a sense that the latter recommendation would be met with this but you don't have the data to answer so I am more inclined to go with the former recommendation.

On the other hand, it is kind of boring repeating a recommendation that has been made 15 years before. I mean, we may feel terribly unoriginal.

DR. CHILDRESS: There may be some other contextual arguments that would be important to consider particularly in the context of public trust and the solidarity of some arguments that play a very different role now in the discussion but one of the things we need to ask, I am very conscious of the time and conscious that our West Coast colleagues, and Hawaiian colleagues will be heading out pretty soon, it will be to see whether we want to get a contract paper and start that process.

DR. MIIKE: I am of the opinion, this is a solution looking for a problem. I am not convinced that this is such a big issue that we must put it forth. I participated in a similar group when the first HIV research projects were being proposed and this was seen as a phenomenally big problem and the compensation issue was what was needed in order to get people

enrolled in research on AIDS. So I am not too sure about, we seem to be talking about this as if we are going to go ahead with it. I would like a discussion about whether we are going ahead with this but there is a charge from the President that says take a look at it, then that is an obligation.

DR. CHILDRESS: And this is not a bad thing to reconsider rather than mandating the request but this is something the subcommittee put on as something to look at. Now the question is whether to contract the paper in this area that would deal with the arguments both as they were presented in the President's commission and earlier and then the ones that have emerged since then.

PROF. CAPRON: And remember, Larry, here we are talking about normal as well as patient subgroups.

DR. MIIKE: Which is not, what we will start getting into is what is the purpose of this and we will start getting into arguments over this will be an exclusive remedy. Is this to be in addition to remaining open to tort suits, et cetera, et cetera, et cetera.

But anyway, one must convince me that there is a problem for which this is the solution before I can really endorse getting into it.

PROF. CAPRON: One of the problems is the absence of the data itself. I mean, that goes back to the point that we decided to send the memo on an hour or so ago and in a way it is

a reflection of the comments we had from Dr. Shamoo this morning about the absence in reports of research of injuries which he argues must have been occurring but were left out of the research report. I don't know what kind of evidence we want. We have had a number of instances. The radiation experiments as an example where after the fact even years later either Tuskegee damages are paid or are being sought for people who suffered very badly. Before those experiments were revealed, one would have said gee, research doesn't seem to involve a lot of injuries and then after the fact millions of dollars are paid because research did involve injuries which were not known.

DR. CHILDRESS: The question is whether we want to recommend having a contract paper in this area and that has been an interest of the human subjects subcommittee so that is the issue before us on this one. Harold?

DR. SHAPIRO: My kind of immediate take on this is twofold. One is I think this is sort of a natural order of things of proceeding wherever this memo takes us. It might be a logical first step to try to find out whether there really is a problem here and how big it is. I understand we don't have the data so we are all guessing but it seems to me that finding out something about adverse effects would be a first step here to find out. Do I misunderstand what we are talking about here? That is just my first feeling. Let's see where that takes us and see what we learn and what is available in that area but

secondly as I look at immediate needs that we have, this seemed to me not to be in the category yet. If we wanted to do this the very next year or somewhere towards spring that seems more effective, I would rather focus on using whatever staff we can put in the field to focus on a problem that we already have and don't know how quickly we can deal with. That is just my take on it but it is not a big issue. I mean, one more paper is not going to make us or break us.

PROF. CAPRON: I agree with you as to staff since we have apparently so few. If we could get a paper it might be al to easier to get a paper that would be due in the fall rather than September so if you think this is on a slower calendar and couldn't be included in the report that we issue this year, I don't think that is, it is not earthshaking whether it comes out this year or next but I think it might be advisable to begin looking around for people to work on it.

DR. CHILDRESS: If you and Alex and other members of the committee feel it is important and we can find the right person, that is, someone who knows something about this and is not starting from the beginning, I would have no objection to seeing what we can work.

DR. COX: I would like to use an analogy. First of all, my bottom line, I agree with Larry. I would like to actually say the same thing. I would like to find out if this is a solution looking for a problem or if the problem is out

there. So a very good analogy and, in fact, in my view led to the President's support of this Slaughter legislation was the public being out there. In this case, the National Breast Cancer Coalition basically saying they would not undertake research studies unless somebody drew a line in the sand with respect to no insurance discrimination. It wasn't hard to figure out that that was a problem.

Then, even when the public was out there saying that, then facts were collected so there have been some recent papers. This is what you are suggesting, Alex. What fraction of people see this as an important problem. It was 20 percent to 80 percent, the different studies of people who saw that as a problem so it was a no-brainer for the President to basically say this is a major problem. It would be a no-brainer for us in some ways. We have to figure out how much it costs but the first step is, is this a major problem. Then there is no question for me, people talked about what the President would do in this is that if there is impediments to human subjects being willing to participate in research, he is interested in getting rid of those impediments because he believes as does much of the public that research is going to be helpful so I think the first question is, is there anybody out there that wants to complain about this.

Secondly, if they do, then how many, what is the extent of the problem and then given that, then Larry it answers both your and

Harold's question. Then it is not a solution in search of a problem but the problem is really there.

DR. CHILDRESS: Okay, can we then think further about the topic and see if there is someone who might be appropriate to do a contract paper? Is that agreeable with the group?

PROF. CAPRON: I think David is suggesting something else which is important which is going to Harris or Roper or whoever and saying would you stick on your next national opinion poll two questions. When research is conducted, do you think it is fair to tell the subjects of the research that if they are injured, they will not be compensated for that? Rewording the question.

DR. COX: I am not sure what the process is.

PROF. CAPRON: We are rewording the question. The second is would you, if you were asked to be a research subject, would it affect your willingness to do so to know, I mean, that kind of a question and I agree with you. If it turned out that there was no public concern, that would be an answer to part of the reason that one would be responding. To me, that doesn't rule out the issue but it certainly could rule the issue in.

DR. COX: Sure. You are not concerned if you are not the one that it has happened to you but if you are the one that has it happened to, you are very concerned.

PROF. CAPRON: Right, and unlike the breast cancer coalition, we know research subjects are generally not a pre-

existing, well-identified body unto themselves. I mean, the people don't walk around saying I am a member of the research subjects.

DR. MIIKE: All I am saying is on a list of priorities this is about 250. That is basically what I am saying unless you can convince me otherwise. I have not heard a groundswell that this is a really big issue.

MS. FLYNN: I would just add, I think it is potentially an important issue. I have not heard a groundswell on it. I am concerned that we not lose our focus and it is complete what we have started to deal with here and then I guess I am kind of where I heard our chair a few minutes ago. I would like to get through some of the things we now have on our list and see where we are and in the process of doing so, we may also discover why this has been recommended repeatedly and never acted upon. Perhaps our strategies for dealing with it will therefore be sharpened.

DR. SHAPIRO: Sounds great to me.

DR. CHILDRESS: In the last 15 minutes, before the West Coast exodus, let me try to cover several things very badly. Part of the, it is not simply a matter, we have a clear-cut set of assignments for the next few months. Part of what we are doing when we are setting priorities is see whether we want to put in place certain kinds of things like contract papers that would then serve as a basis for our reflections into next

year. Here, let me just quickly mention some of these things and some of the matters I think we will just have to circulate, for example, some drafts of proposals for contract papers or one that is already on the way.

IRB studies, the building of trust indicates that NBAC is actually looking at the IRB system and will make recommendations for a form this year. The two studies that are underway, we will have some information from, at least one area of information from, I have talked with the key figures in both of those, Charles McKay and also the person down in Miller's successor on this particular project in the Office of Inspector General, they will have preliminary data on it at the end of the year. Maybe they will share something with us a little before that and Charles McKay, you will be providing preliminary material in the fall so I am still not convinced and I don't know what the group thinks, that we are at a point we could even talk about planning an IRB study without knowing what we have from these.

Is that a general feeling? Alex, do you feel comfortable with that? Once we get this material, then we could go ahead and see what we need to do.

One of the groups we plan to talk about, children and adolescents in research, I have asked Diane Scott-Jones and Arturo Brito to head our efforts in this area but since this is something for next year, in the shortness of time I will ask you

to circulate descriptions to us as to how we might proceed, whether we need to be thinking about contract papers and so forth given our 14 minutes left. Is that all right with both of you?

We have two other items that need to spend a little time on. One is Bill Freeman's emergency research discussion. This is a case study. I recall that we are not asking indeed a charter as well as an executive order that indicated that we would not look at cases to approve or disapprove but rather would use them at most as illustrations so the broad principle we are expecting to consider.

Bill has proposed that we think about a case using what is prepared on this particular case study on emergency research to think about some broader issues and then we have circulated to us a memorandum from Dr. Sidney Wolfe and colleagues about the study, the placebo controlled study of HIV transmission from pregnant women to children and again that is not something we would look at as an independent study given our charter and mandate.

On the other hand, each of these may raise some broader questions of principles involved in international research or principles involved in defining risks or in how one does public ethics, the last two being in relation to emergency research.

So if I could ask Bill to just, I hope everyone has had a change

to look at that and Bill, we will only be able to take three or four minutes on this and I guess one thing I would like to say at the beginning is that one can distinguish in Bill's discussion two major sorts of concerns, one having to do with a process, how one changes some fundamental concepts and categories in bioethics and how one functions in public or in private versus the risk one.

Now, on the risk one, this is going to be something probably we need to look at for cognitively impaired research subjects for children and so forth. That is, a lot of the conceptual and normative questions surrounding risk need a lot of attention but Bill, in our brief time --

DR. FREEMAN: As everyone has read it, I want to emphasize I am not suggesting reopening the issue of emergency waiver, waiver of consent in emergency research but to use it as a vehicle for these other three items and you handed out a one-page memo about, that gave some possible practical first steps in each of them.

The one, and they just draft. This is just to say there are some steps we can think about. The one that is certainly more pressing is the question of risk which is the first section on the memo today. When I passed around earlier drafts of the first memo you got, a seven page memo that looked at this, IRB members are saying yes, we really do have a problem of understanding risk. The current definition, there is

actually two competing definitions and there is problems with each one as I said in the memo.

And the question of risk is so important because it has up to now been the barrier that stopped slippery slope of considering the benefits to society outweighing the risks to individuals in research, that you could not do that without, it was greater than minimal risk, without the consent of the individual. That barrier has been in effect changed for the emergency waiver of consent and emergency research but the point is that that is such a critical element in the regulations, the definition of minimal risk for protecting people that if there is confusion, it seems to me not only is there confusion, there is problems with either of the competing definitions.

This commission would serve a great benefit to IRBs and to the system to clarify that.

DR. CHILDRESS: We will reserve the other part, Bill, for discussion but my sense is that this would be an important area, again for just what we are doing for cognitively impaired research subjects to try to get some clarification on it, to get some conceptual work and if there is agreement on that, I would like to proceed to trying to get a contract paper in this area.

DR. SHAPIRO: Could you just clarify for me, Jim or Bill, what we are really focusing on? Is it actually the definition of risk? Understanding what we mean by minimal risk? Or is it something else? I am not sure I am getting the point

here.

DR. FREEMAN: Is it actually several things rolled up into one. There is the definition that says risk is, in effect, what is experienced in the daily life of people who are going for examinations and the question is what are the people. If they are the normal people, then you have as the standard of comparison, then if you are doing, say research on a biopsy, as my example was, in the middle of an operation, people getting an operation for other reasons, just plain medical care, abdominal operation just to do a snip of momentum, fatty tissue in the abdomen. That is greater than minimal risk because you and I don't have operations. So that doesn't make sense because in fact the risk obviously is minuscule once it is in that context. But the other point is if you say okay, it is the, the risk is of the people experiencing the research, you have the anomaly that people who are sicker can have more severe research done on them. People who are close to death can have almost any research done on them because it is not greater than minimal risk and it can be done without their consent. That doesn't make sense either.

The two competing definitions don't seem to reflect reality and it was behind the problem with the labor and I can tell you, listening to IRB members that it is still a big problem trying to understand what we mean by minimal risk and again, it is a linchpin in the regulations. That is one problem.

The second problem, my perception is, it is a little bit more than just risk. It is that the Belmont report and the regulations, are they comparing risk of individuals to benefit of society or risk of individuals to benefits to those same individuals participating in research? I think that also has shown some confusion, and it has shown confusion especially in the cognitive, whatever term we are going to use, research. Some of the controversial research may be controversial because they were looking at benefit to society in weighing the IRB, in weighing the issues not benefit to the individual and to the risk to the individual outweigh the benefit to (word lost) so, do we want to address the substantive. Actually three issues, the substance of the confusion and then finally if, having done so, how do we think that our interpretation would become accepted and conveyed to the IRB community because I agree with you, your memo illustrates beautifully why there would be confusion on both of these points.

DR. CHILDRESS: One question is whether, it was raised while you were out. It is something we want to ask Bill to focus on in terms of perhaps drawing a possible description for the paper.

PROF. CAPRON: Does he have time to do that with everything else? Compliance study is higher priority.

DR. CHILDRESS: It is higher priority.

DR. SHAPIRO: This does strike me as a central issue I

have to say. Just how we want to time it I am not sure but it is important.

PROF. CAPRON: If it is not Bill, someone should certainly write about this.

DR. CHILDRESS: I wasn't asking Bill, just to start a description.

PROF. CAPRON: He has written it. There is the description of the issue. The risk-benefit issue is not in this memo. That is another paragraph.

DR. CHILDRESS: The description for someone to write a paper.

DR. SHAPIRO: I think that would be very useful.

PROF. CAPRON: Did you address the second point yet?

DR. CHILDRESS: Basically the first point because you folks are, I don't know if you are going to leave immediately so what we are going to do is put the public and the fundamental changes in bioethics for a later discussion.

PROF. CAPRON: I just want to say, I did not think your narrative here illustrated a problem with public bioethics. It illustrated a problem with the federal agencies not knowing what prior federal agencies and commissions have done.

DR. CHILDRESS: I will have to cut this part off because we are getting, before you folks leave, some discussion of the other, Bill will proceed with this part and it will turn back to the other issues raised but tin the last few minutes,

and I hope you folks can give us a few minutes past three before you rush out, is the issue of international research.

Now, this is something that has been raised before as to whether we have double standards involved in research, the U.S. funds and sponsors in the U.S. versus research and sponsors and funds abroad. And of course there is this particular case that has been raised.

The question that is before us is whether in the light of such cases not to deal with such cases but in light of such cases, we want to make this area something we deal with over the next several months, not something we try to deal with before the end of the year. But is the conduct of research abroad, research that the U.S. funds have sponsored something that we would like to include and all are familiar with the controversy again that was included in your packet. I won't go into detail. But we will hear in a public session, in the public testimony which we will start in just a few minutes, Dr. Sidney Wolfe is here and will be speaking at that point.

But any thoughts now?

MS. FLYNN: On that issue?

DR. CHILDRESS: I am sorry?

MS. FLYNN: Thoughts on that issue?

DR. CHILDRESS: That is to whether this should be one of our priority topics.

MS. FLYNN: I guess I feel sort of strongly that based

on our own knowledge which is often the best way to feel strongly, especially late in the day, it would be difficult for this commission, especially given the visibility we have had to be promoting strengthening of various protections and ethical standards in this country and ignoring or seeming to implicitly permit some other standard in research that is going on or received so to me it is all part of the piece and given what we have seen, I think it is important that we take a good look at it.

PROF. BACKLAR: I want to second that because in case this conversation goes further, I agree.

DR. MIIKE: And I agree as well.

DR. CHILDRESS: We don't have disagreement then. Anyone disagree?

DR. SHAPIRO: I don't know if I disagree. I don't think it is all that obvious. I think it is probably correct but I think there are serious issues.

DR. CHILDRESS: But the federally funded --

DR. SHAPIRO: Federally funded research taking place somewhere else. I would like to hear the arguments. I mean, I understand this is probably not correct but --

DR. CHILDRESS: The issue is whether --

DR. SHAPIRO: I don't think it is just so obvious that we can fall off a log and say gosh, let's all sign up.

DR. CHILDRESS: But the real impression is whether we

address this area and make it a priority area. That is all we are interested in now. Not the conclusion but something else to be addressed.

DR. SHAPIRO: Yes, and the surest way to address it is to ask the agency who has funded such research to address the reasons why the criticisms are not as persuasive as they seem, as a starting point. It is not as though we don't have rules that talk about this research. This type of research --

PROF. CAPRON: I think Allison made a very good point. One, we have the capacity that asks agencies to respond and it seems to me this is ideal territory for us to operate in.

DR. SHAPIRO: Making clear that as Jim has said, we are not asking, we are not suggesting that we are going to criticize the approval of any particular protocol that we see this as a problem, potential problem area and we want to jut know what the lay of the land is and what their response is to criticisms of this sort.

DR. CHILDRESS: Okay, is there agreement on that, Bill?

DR. FREEMAN: Just a point. We passed out an earlier memo about the issue and the issue is in part a philosophical one I think. Is the word, quote, same, unquote, in reference to the same procedures in a different context or to applying the same rules in a different context and ending up with a different set of procedures. It may be worthwhile to ask both the public

citizen and the public agencies to respond to that almost with an identical letter because otherwise I think they might be talking past each other.

PROF. CAPRON: We should also as a suggestion to staff request from the Council for International Organizations of Medical Sciences its international guidelines for research and its international guidelines for epidemiological research and for the papers that emerge from a conference that was held on that topic in which people like Larry Gosten from Georgetown addressed this very question of how one conducts studies in other countries that are respectful of their ethical standards as well as congruent with sponsoring countries.

DR. CHILDRESS: And then when we receive this material we will make some judgment about what next steps to take. So we can get a contract paper or contract papers.

Any last items? I know the --

PROF. CAPRON: I want to apologize, by the way, to the way the public comment is scheduled here. I for one will read the transcript with interest and I am sorry I won't be here to hear it firsthand.

PROF. BACKLAR: I would like to apologize, too. I feel very concerned that we are leaving.

**Agenda Item: Statements by the Public**

DR. CHILDRESS: If you have five minutes, we are going to turn to this right now so you don't even have to go out in the middle

of the comment. My understanding is that we have one person, Dr. Sidney Wolfe, to make a public comment. Is there anyone else who wishes to make a public comment? If so, we will schedule you right after that. We have asked Dr. Wolfe to take five minutes in presenting.

DR. WOLFE: I have this bachelor's anxieties to deal with.

DR. CHILDRESS: Dr. Wolfe, one particular West Coast person is anxious to get to the airport so she is --

DR. WOLFE: I originally discussed this with Tom Murray and then with a number of other people and they thought at least raising this as Jim mentioned as the larger issue of conduct of experiments in foreign countries. One part that Harold Shapiro alluded to is federally funded and there is another part that has to do with the U.S. government which is situations in which a drug company does a foreign clinical trial but then uses it in the United States to gain approval for a drug because of a lack of resources and so forth and the FDA doesn't have as much attention focused on the conduct of those trials and yet if a different ethical standard is used in those trials, we still have, I believe, a problem.

I would just like to raise some of the general issues which affect both categories, the federally funded research which is NIH or CDC and the research through FDA or possibly even through EPA. The questions that I had which we certainly

thought about when we focused on these studies done in Africa and Dominican Republic and Thailand on attempting to interrupt maternal child transmission of AIDS were one, how much prior knowledge do we have of effective treatment and related to that, how serious would the problem be if we withheld effective treatment as in the placebo?

Secondly, what is the standard of care in those countries? That is an issue that has been raised. I would change that to what is the possible standard of care because if we are doing an experiment in another country, we are hoping that even if the current standard of care is one thing, that if the experiment works such as in the HIV-AIDS, they would be able to change the standard of care.

Third, is the right research question being asked? Whenever a placebo controlled trial is done, the question is, is something better than nothing and the answer is mainly going to be yes. In several of these other instances both FDA drug studies and some of these NIH studies, the question should be is our new therapy as good or almost as good as the old therapy I would believe.

And four, could you or would you do the study that you are planning to do or doing in a foreign country in the United States? What would happen if you tried to do it and if you wouldn't, what is the answer? Why not?

So I would like to spend the remaining three minutes

then just going briefly through two case studies and they are just illustrative of, I think, a much larger problem which is what I hope you all would be interested in.

One, the studies, seven funded by NIH and two funded by CDC, in which there is an effort to try and reduce the maternal child transmission of HIV. Three and a half years ago an NIH funded placebo controlled study showed that you could reduce by two-thirds the transmission by giving what was called protocol 076 which now is the gold standard in all the developed countries. Understandably there was an issue in developing countries to try and see whether we could do something that would help them as well and knowing that they couldn't afford the gold standard, efforts were made to develop protocols that were not as complicated, as expensive and as extensive for them. The question was not should you be doing studies in these countries but should you be comparing the modified regimen with the gold standard or with a placebo. There is a very sharp controversy over this, not just related to the analyses that we have done. For example, the CDC says essentially you have got to do a placebo-controlled trial in Thailand. It is unethical not to. The head of the Harvard IRB which is doing a non-placebo controlled trial says it is unethical to do a placebo controlled trial so you have got diametrically opposed views, one funded by the CDC, one funded by the NIH.

Researchers in some of these countries, although they

are said to be very compliant in the memo we handed out to you, can see there is some serious question amongst Ivory Coast researchers and we have subsequently found in researchers in Zimbabwe and elsewhere.

So that is an example, at least in terms of the government-funded studies where there are sharp differences of opinion and those studies reverted back to a statement issued by CDC working group or by a WHO working group in the summer of 1994, six months after the completion of this, the interruption of this protocol 076 that said the best way of doing this is placebo controlled trial. It has never been published and the validity of it is somewhat questionable. A number of people who disagreed with that viewpoint were not invited to the meeting. Finally, I would just like to end with examples in the FDA area. Back about seven years ago, it was shown conclusively using randomized placebo controlled study that we took older people with so-called isolated systolic hypertension, blood pressures over 160 and as high as 220, that by giving them effective anti-hypertensive therapy you could reduce significantly the incidence of stroke and other cardiovascular events. From that point on, the standard of treating such elderly people is to give them an anti-hypertensive drug.

However, right now and recently and in the future, studies funded by drug companies in this country and ultimately to be included in the application for approval of a drug are

doing placebo-controlled studies. One is in China. One was supposed to be in Western Europe. They couldn't recruit enough people so they used a lot of people in Eastern Europe and they are basically giving it to people with blood pressures as high as 220. Half of them get a placebo and half get anti-hypertensive therapy. The FDA finds out about these studies around the time they get submitted for FDA approval rather than finding them out at the beginning where they would, with an FDA study, a study intended for FDA approval, is done in this country.

So I just will close on that. I think I have taken five minutes. I think there are a large number of other examples in the AIDS area, in the clinical trials on drugs that really raise the question are there different standards in other countries? Are they justified? What would happen if we did these studies here because in some cases we would learn a fair amount from doing the studies here, just not placebo controlled studies. Ultimately in this country we don't have enough money to be giving out the gold standard treatment, protocol 076, to everyone if we could come up with a less expensive dose, if would be useful here but we wouldn't do a placebo-controlled experiment here.

Anyway, I will stop on that note. If there are any questions, I hope I have not extended beyond the five minutes.

DR. CHILDRESS: Thank you very much and thank you for

respecting the time limit. Sorry we lost some of our colleagues in the process.

Since there are some questions, I have one that relates to our previous discussion. I am assuming that you would be willing to respond to the kind of inquiry that was suggested earlier.

DR. WOLFE: Certainly.

DR. CHILDRESS: And second, I would also invite you and your group to submit any materials you would like since you have heard now the kind of process that we would follow to look at the general issues that are involved in this kind of research.

DR. WOLFE: Do you have some sort of time frame in that?

DR. CHILDRESS: I am not sure. Not when you came in but we have been setting some priorities.

DR. WOLFE: Just get back to us and we can respond fairly quickly.

DR. CHILDRESS: That is fine. It is not something we would be taking on immediately.

DR. SHAPIRO: It is not weeks. It is months.

DR. CHILDRESS: No, it is not weeks. Other questions or comments? Okay.

DR. SHAPIRO: I just want to say I found the material I received really quite helpful, very clear and descriptive and

focused me on the point easily so I thank you for that.

DR. WOLFE: Before we got into this, my background is more academic. I come from NIH originally. We ran this by a number of ethicist ranging from George Annes to others to see what they thought about it. There was a lot of concern. I think that although it happened with a minimum amount of controversy, when people become aware of it, it is clearly controversial and I think the larger issue is one that I don't think has adequately been addressed. For WHO to just sort of throw out their placebo-controlled trials the best way just doesn't work I think, and there are too many people opposed to it to think that it is settled.

NIH is right now considering funding more such studies so it is really a matter of some urgency and FDA, I am going to be meeting with them, asking what their protocol is for lately looking at these kinds of things.

DR. CHILDRESS: Again, thank you very much. Mr. Kavanaugh-O'Keefe would also like to testify.

MR. KAVANAUGH-O'KEEFE: Thank you very much, Dr. Childress. I just want to call your attention to two things dealing with the issue of international studies and what can be done there. One is, it is a web site, it is www.africa2000.com. It is the site for the information project for Africa which has among other things a series of perhaps 50 studies of EIB contracts in Africa in the last 20 years or so and looks at

frequently. Most of it is looking at the issue of the difference between how the studies are conducted in the United States and how they are conducted there.

The second thing I just wanted to call your attention to the BBS documentary from October of November 1995 called the human laboratory. It is a study of American funded drug trials in three countries including Haiti and Bangladesh. I guess the third was the Philippines. It is the human laboratory. I can mail a transcript to everybody on the commission. Thank you very much.

DR. CHILDRESS: Thank you very much. Is there anyone else from the public who would like to testify? Members of the commission, Dr. Shapiro, anything else to add?

DR. SHAPIRO: No.

DR. CHILDRESS: Well, we thank everyone for his or her patience and perseverance.

(Whereupon the meeting was adjourned at 3:14 p.m.)