NATIONAL BIOETHICS ADVISORY COMMISSION

HUMAN SUBJECTS SUBCOMMITTEE

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I N D E X

P R O C E E D I N G S

OPENING REMARKS BY CHAIR

DR. CHILDRESS: Let me welcome members of the Human Subjects Subcommittee, staff and also members of the audience. We are pleased to have you with us today as we begin our discussion about and deliberation regarding ways to respond to issues in human subjects research.

This, I think, will be an interesting day but it will also be an arduous day. We have a lot of topics to cover and we have a difficult task of trying to set priorities for our work over the next several months.

We will have an occasion for public comment at the end of the day and if you are interested in making a comment please see Pat and sign up, and we will work you in sometime around 3:00 o'clock today.

Before we get started I would like to have the members of the subcommittee introduce themselves and then we will go around the room if no one objects and ask each person to indicate his or her name and also institutional affiliation.

Rachel, shall we start with you?

DR. LEVINSON: Sure. I am Rachel Levinson and I am the Assistant Director for Life Sciences at the Office of Science and Technology Policy.

DR. MANGEL: I am Joel Mangel. I am part of your staff.

DR. FEINSTEIN: Good morning. I am Emily Feinstein and like Joel Mangel I am also a part of your staff.

DR. CASSELL: I am Eric Cassell. I am an internist at

Cornell.

PROF. CHARO: I am Alta Charo. I am Associate Professor of Law and Medical Ethics at the University of Wisconsin, Schools of Law and Medicine.

MS. FLYNN: I am Laurie Flynn. I am the Executive Director of the National Alliance for the Mentally Ill.

DR. CHILDRESS: I am Jim Childress. I teach biomedical ethics at the University of Virginia.

MR. DOMMEL: I am Bill Dommel. I am Acting Executive Director of the Commission.

DR. _____: (Not at microphone.) (Inaudible) Executive Officer, American Society of (inaudible).

DR. MOORE: Debbie Moore, Office of the Director, Office of Recombinant DNA.

DR. _____: (Not at microphone.) (Inaudible), NIAID, Office of (inaudible).

DR. HARRIS: Alan Harris, Naval Medical Center.

DR. _____: (Not at microphone.) (Inaudible) OPRR.

DR. _____: (Not at microphone.) I am Manny (inaudible). I am with the Urology Institute of NIH.

DR. _____: (Not at microphone.) (Inaudible), Food and Drug Administration.

DR. TITUS: (Not at microphone.) I am Sandy Titus. I work in Human Subject Protection (inaudible).

DR. ENGLISH: Charles English from the Department of Defense.

DR. THOMAS: Suzanne Thomas from the Biotechnology Industry Organization.

DR. CASPARUS: George Casparus of OPRR.

DR. _____: (Not at microphone.) (Inaudible) Andrea (inaudible).

DR. _____: (Not at microphone.) Irene (inaudible) Research Service.

DR. _____: (Not at microphone.) Doris Goldstein, Kennedy Institute Library.

DR. MURPHY: (Not at microphone.) Kate Murphy, Department of (inaudible).

DR. NORRIS: Good morning. I am Pat Norris with the commission.

DR. QUINLAN: (Not at microphone.) (Inaudible) Quinlan with the commission.

DR. ELLIS: Gary Ellis, OPRR.

DR. TBILISI: Tom Tbilisi, OPRR.

DR. _____: (Not at microphone.) (Inaudible).

DR. DUNCAN: Katherine Duncan, OPRR.

DR. AKIN: Diane Akin, OPRR.

DR. McARTHUR: (Not at microphone.) Ann McArthur, (inaudible) Center.

DR. CHILDRESS: Welcome to everyone.

Bill, is there anything you would like to say?

MR. DOMMEL: No, I will reserve my remarks to introduce the team that is going to be working.

DR. CHILDRESS: Rachel, anything?

DR. LEVINSON: No.

OVERVIEW OF PROCEDURES AND TOPICS FOR DISCUSSION

DR. CHILDRESS: All right. Let's spend a few minutes talking about the procedures and the topics. As I mentioned, our goal is to set priorities for our work over the next several months and depending on how long we exist maybe over years.

Obviously one of the difficult questions in setting priorities is to decide what criteria are appropriate for determining priorities. One simple thing is to do what is do-able. Another obvious thing is to focus on what is most urgent and what is critically important. Another is to focus on what is mandated. Part of what we will do this morning is hear a progress report on one mandated task. Another is to determine what has to be done before we can do anything else and what kind of information we need. There are other possibilities as well.

We have circulated to NBAC as a whole a list of topics for consideration under the general area of human subjects research and have gotten feedback and suggestions from a variety of people about other topics to add, ways to arrange them, structure them and so forth.

As a result of that discussion I have circulated and prepared as part of the agenda a list of the materials at 9:30 a.m. and at 10:45 a.m.,a laundry list of topics and others that are not included there and obviously one of our further topics today is a discussion of IRB's actually does not even appear on that list.

But as we work through these topics one thing we have to decide is which we think really are most important for our purposes and

when to do it. So it is -- by the end of the day hopefully we will have some sense of where we are going over the next several months and a work plan we want to report to NBAC at our January meeting in just a few weeks.

Now before we get into these topics and try to determine which ones we want to focus on in our work plan and how to go about that in our work plan, I would ask members of the subcommittee to present some of their general perspectives on what we are about, some of their aspirations and hopes, some of their fears and concerns, in effect to get some sense of where our subcommittee members are coming from as we approach this topic.

Welcome, Arturo Brito. We are glad to have you join us.

I think I will start with Alta who had circulated a memo in our discussion on the Internet and to share some of her thoughts.

PROF. CHARO: Yes. I found that as I was reflecting on the first meeting, I am sorry I missed the second one in San Francisco, that I was still confused about some really basic things. Jim was kind enough to actually put it on a copy of the e-mail because God knows I write enough that I cannot keep track of it.

The first was that as we were working through the agenda possibilities last time I found myself still unsure about the target audience for our work and that seems to me to be an important question before we actually set down what work we would do. I would like some guidance actually from the people who were involved in drafting the charter on this.

One of the obvious possibilities struck me as being the programs for the agencies, the Congress, the general public in kind of a fashion. And unlike the President's commission that Alex had worked on, if

I understand it correctly the NBAC is situated entirely within the Executive Branch under OSTP through the White House and the recommendations that we make are made to the agencies, and the only enforcing action we have is for the agencies to then respond to the recommendations. So that at first blush it struck me that the target audience was the agencies under the Executive Branch.

I still find myself wondering whether people felt that there were other audiences that were as important or more important and whether we should be targeting them because that would change the nature of our work we would do. That is question number one.

And then just as the previous question, number two -- question number two had to do with who would then implement anything that we might recommend.

And then the third had to do with kind of the organization of discussion and whether we would want to start with broad questions that would provide agency guidance as they do their continuing regulatory reforms to their existing mechanisms. Things like questions of do you want a study on protection. Like do you want to have a continuation of a decentralized monitoring system or do you want to change to a more centralized version as opposed to trying to tackle individual specific issues, whether it is a particular subpopulation that is not yet covered in the regs, et cetera.

The first one in terms of target audience, the question goes to the people who developed the charter as well as the commission, what they think would certainly help me a lot.

DR. CHILDRESS: Okay. Before we turn to others, any

response to that, Rachel?

DR. LEVINSON: Yes. I would be happy to respond to that and that is a very important question. Your first question about the target audience. It is true and you are speaking as a lawyer and it leads me to try to answer it precisely to begin with and then more or less digress.

The commission officially reports to the National Science and Technology Council, which is a body administered by the Office of Science and Technology, but it is chaired by the President. So the idea is that it reports to this committee, the National Science and Technology Committee, to the President directly as the chairman, and it is made up entirely of Executive Branch agencies.

So it is advisory to the Executive Branch but a very important part of its mission is that it open public meetings that allow the opportunity for discussion with the public and this is an official meeting of the National Bioethics Advisory Commission. As such it is announced in advance in the Federal Register and through other means as a way of gathering public input on issues that absolutely require public discussion.

So that even though it is reporting to the Executive Branch it is constructed in a way that is intended to bring in the voice of the public. Part of that is also that it can accept for consideration suggestions of issues from the public, from Congress, from the Executive Branch agencies. The charter was constructed also in consultation with members of Congress who were very interested and so it is intended to provide them both access and advice and guidance.

So even though administratively it reports to the Executive Branch it is intended to provide for wider discussion than just within the

Executive Branch.

DR. CHILDRESS: So broad input from Congress and the public as well as the Executive Branch, and then kind of funneling through the council but with the assumption that the implementation then would be spread out as appropriate depending on what emerges from the council.

DR. LEVINSON: Exactly. And to the extent that recommendations can be implemented administratively by the Executive Branch that will work. So even though you are correct in saying that the forcing clause applies only to the Executive Branch that is because that is the only way legally we have a mechanism for it to operate. But there are members of Congress that are interested and suggestions that could only be implemented through legislation can come back through that route.

PROF. CHARO: And as far as we are concerned is there any feeling among people who have been sitting on this thing now for a couple of months where we ought to direct our energy? I am only asking because I am in such a muddle.

DR. CHILDRESS: Well, I think that perhaps apart from the answer we just heard a lot would depend on what we think about the appropriate direction of particular topics, that is some of these will be more appropriately implemented by some groups rather than others, and some may just be to develop guidance that actually may be as much for investigators and the public say as for actual implementation from a governmental context.

But other thoughts?

DR. CASSELL: Yes.

DR. CHILDRESS: Eric?

DR. CASSELL: Well, first I have been thinking about this a great deal because the first item is the audience is everybody because by the nature of the media and everything else anything that is said here begins to be disseminated and it has its force not only in the fact that it goes to a larger audience, but that the audience is responsive. So it comes back in, in terms of modifying what we do and how we think about it.

But in the same sense of this as an ongoing process I have that same feeling about the research endeavor. I would feel badly if we found ourselves as a commission duplicating or making points finer that have been done by commissions before us like the points in the Belmont Report or something like that because I think that would not be -- that is not necessary. There are other people that can do that. That is what regulations are about. That is why small groups sit down to hone regulations.

I think what we have to see is it is now 20 -- the Belmont Report was '78, right? Something like that. Yes. So it is almost 20 years. Certainly 20 years since the commission operated and started going. What we have to see is what has happened to the research establishment, its relationship to the country in which it sits and its potential subjects that might change our direction at this time as opposed to what we might have done 20 years ago.

I want to talk about their informed consent and I will be more concrete about that. But we are in a different nation than we were. The research establishment is vastly different than it was 20 years ago, certainly than it was 30 years ago to which the 20 years ago thing was responding. There is always that slowness in understanding.

DR. CHILDRESS: Speak a little louder.

DR. CASSELL: So I think that what we have to try and see is what has happened to the research endeavor. What has happened to the population called subjects and what has happened to the population around this endeavor that now changes the direction of our work. I think actually it changes it considerably. As I said, when I talk about the issue of consent I am going to be much more concrete about it.

But I think if I had to put it in one sentence it is a changed world that changes our function and our function has to do with the relationship of the nation, its research endeavor and its subjects.

DR. CHILDRESS: Thanks. Arturo?

DR. BRITO: I agree that it is a changed world but one of the things we have to be careful with is that I am not sure mankind has changed all that much. I think one of the things we need to look at when we are worried about subjects or people as subjects in research is what are the similarities between what is going on today and what has gone on in the past that has set up a scenario where human beings were treated unjustly in research.

So I agree with Eric that it has to change broadly. I think we need to look at the similarities because I think that will help us in guiding us to determine how best we can advise -- or I guess the public. That is where I think would think we are really going even though we are going through the Executive Branch.

MS. FLYNN: I would just add that it seems to me that we are dealing in an environment which is tremendously important that we take a very good and thorough look at this area. The general public is both

more aware and I think more confused about what actually are the protections for human subjects. I think that the research enterprise has become very complex. I think that there is some concern as to how well human subjects protection is appropriately safeguarded in all settings. I think there is some concern about the degree to which the principles articulated in the Belmont Report are, in fact, transmitted to those who are in charge of the research enterprise.

So I think we have an important opportunity to engage the public in perhaps a more thorough way than has been previously possible because I think members of the general public are more and more aware of the promise of research and the potential for really compromising vulnerable subjects in research protocols.

I think we are faced with a great deal of need for knowledge that has not heretofore been gathered. The principle unit that we rely on for protection of human subjects, the Institutional Review Boards, are to me and I think to many others somewhat of a black box. We really do not have a clear understanding of how they are operating across the country. I think many of us have a sense that it is quite highly variable.

So I think we do need some basic information in order to scope and frame how we will then be able to proceed as has been previously discussed to take a look at how we update, inform, revise or reaffirm those practices and policies that are already in place.

DR. CHILDRESS: Other points that people would like to make?

We will obviously be coming back to a lot of these in more concrete detail later. Each of the points that has been made I think will be

an important part of what we are discussing today with particular attention to Alta's first question about target audience as we proceed through each topic since I think the audience will vary again depending on the topic.

We have had a request for each of us to speak louder. So would you please, if you cannot hear us, if someone would just signal. That will let us know that you want us to speak up. Thanks.

Anything else from the subcommittee members before we turn to our first topic?

Okay. We got through those first general perspectives much more rapidly and got started in time so we are actually ahead of schedule which will not remain true for the day. But we will take advantage of this for the time that it has provided.

I will ask Bill Dommel to take the lead in this next part of the discussion, which is "Preliminary Evaluation of Federal Agency Reports on Human Subjects Protection." This is a task that was mandated and that has been underway.

So, Bill, I will let you introduce our other panelists.

PRELIMINARY EVALUATION OF FEDERAL AGENCY REPORTS ON HUMAN SUBJECTS PROTECTIONS

MR. DOMMEL: Thank you, Jim. Good morning.

This is one of our mandates. A mandate to the commission and then subsequently to this subcommittee for lead in assessing what was required by the President in Executive Order 12975, October 3rd of 1995, which established the commission, and which said that "each department and agency that conducts or supports or regulates research involving human subjects shall report the results of a review required by the

Executive Order the implementation of protections of human subjects."

We have what is referred to as the "Common Rule" or as the "model federal policy" for the protection of human subjects, which was adopted by perhaps all or nearly all the federal agencies which conducts research involving human subjects in 1991, I believe. And subsequently established in accord with the recommendations of the President's Commission of the early '80s the committee of representatives of each of the agencies carrying out such research and chaired by the director of the Office of Protection from Research Risks in the Department of Health and Human Services.

So the opportunity here is that given a regulation, a set of regulations issued by each of the agencies carrying out human subject research in the federal government, that each of those agencies have issued regulations in accord with the Common Rule, and that Common Rule is almost identical to Subpart A of Department of Health and Human Services regulations for the protection of human subjects, which have been in effect in the current form almost exactly since 1981 and in many ways since 1974, but only introduced federal-wide in 1991.

So here an opportunity to look at the agencies' descriptions of their implementation of these policies. And those reports required by the Presidential Executive Order were to be filed by this commission. They have been and as a first step Jim has asked staff to evaluate those reports and make decisions on follow ups to that initial evaluation.

We were able to obtain the volunteer assistance of a former deputy general counsel of the Public Health Service with a great deal of experience with the development of these regulations over the decades to

work with the commission on a volunteer basis and with the volunteer assistance of Emily Feinstein.

So the former deputy general counsel to the Public Health Service, who is now retired but working with the commission, is Joel Mangel.

Joel, why don't you tell us a little bit about what you have done in the past on these regulations and then introduce us to your current assessment of the agency report?

DR. MANGEL: Sure. Hello. We are your staff and since this is our first chance to meet each other I guess it is appropriate for me to say a little bit about myself.

Can I be heard at the other end? We are really off on an end here.

Well, in addition to working in the general counsel's office in this department for 30 years I have been actively involved in the human experimentation area for almost all of those 30 years starting back in the late '60s when I actively was -- I was actively involved in the drafting of the first department's policies, the Grants Administration Policies on Human Experimentation, which really are fundamentally the same as the Common Rule.

They introduced -- well, they did not introduce the concept of informed consent, but they centered on informed consent and made the Institutional Review Board the centerpiece of the activity, and pretty much formed the basis of the rule which has been, of course, updated and made much more sophisticated in the intervening years.

I also served as the legal advisor to the Tuskegee Syphilis

Study. That is the group that studied the study, not the group that conducted the study. And from '74 to '78 I was the legal advisor to the National Commission on Biomedical and Behavioral Research, which I would add was one of the most impressive organizations I have ever served with, and produced the Belmont Report, which you referred to. I have stayed very actively involved in all of the intervening years so I bring a fair amount of experience to this particular task.

Then with me is Emily Feinstein. Emily, why don't you tell us a few things about yourself?

DR. FEINSTEIN: I recently graduated from Brown University. I majored in biomedical ethics. So I have come here to join and work as part of the staff beginning in October and I have been assisting Joel.

DR. MANGEL: I just have a little to add to Bill's description of the task. I also would perceive this task as finding out from the agencies not just the extent to which they are complying but the problems they are having and what kinds of recommendations they might have for us for improvement.

Now what I would like to do this morning is tell you what we have done so far, what we have learned so far and what we think needs to be done next, and then since we work for you find out from you what you think of all of that and what you would really like us to do.

Now what we have done so far I have kind of divided up into administrative tasks and substance. Administratively we have been working on just getting us up and running. And since I am part-time and Emily is new to all of this, our number one priority has been to hire

someone to lead this effort. We have been interviewing actively and would hope that we will be able to find someone.

One of the problems, I think, is a problem that any new organization has. We do not have a track record and we do not have -- there is not a whole lot that is certain and the really good people are people who have good jobs already. So it is one of enticing someone into a new organization. But we are hopeful that we will make some progress. If we are unable we may be coming to you folks for some recommendations. We have had a number of feelers out. But that is our number one priority because I do not think we can really get up and running until we have someone to lead this individual task.

Now substantively we have received the responses from the 16 federal agencies that have committed themselves to the Common Rule plus a number of other agencies that have written in. I want to give you my impressions of those responses but I want to preface it with an admonition and that is that this is really an impression that we formed off of a quick reading.

None of this should be deemed as being accusatory or pointing fingers at agencies for noncompliance and certainly I would urge those of you who have got pens poised to listen and to take that seriously. We have not found any great evidence of noncompliance but there are some concerns that we would like to share with you.

First of all, one is impressed by the unevenness of the responses. Some of them are quite wholesome. Others are simple statements of compliance. Now to a great extent this varies with the amount of human experimentation that might be going on and the degree

of sophistication. But there is an unevenness and while all of them are aware of the -- show an awareness of the responsibility to comply with the Common Rule, as you read through them certain questions arise.

For example, there is a threshold concern of who in each agency or what entity in each agency is making the decision as to whether or not human experimentation is being conducted. It is one of the advantages of living in Washington and reading the Washington Post. Two agencies, one of which would assert that it was doing no research, another which would assert that it came under one of the exceptions, and in recent days have had press releases indicating new programs which at least to my eye show that some kind of research involving human subjects is going on.

Here I think that what we might be seeing is perhaps agencies where the people who are in charge of the Common Rule may not be aware of everything that is going on in their department. Not an unusual kind of a thing but it is a concern and one of the things that we really should be looking into is where is the focus of each agency and what kinds of access do those people have to the decision makers within the department.

One of the things that has always concerned me, both in my former life and in this task, is the extent to which monitoring is being conducted. It is one thing to have policies in place and quite another to find out whether or not it is actually working. Here I think there is a combination of problems. We are in an era of fiscal constraint. We are in a time when staff is cut back. So agencies have got to confront some very real decisions. Do they monitor exclusively based on reports? Do they do some -- how much education can they do and how much actual

prophylactic kind of monitoring can be done?

As one goes through the reports again there is great unevenness. I think that all of the agencies indicate some monitoring but I think that some more examination of those issues could -- we could benefit from that.

Which brings me to a related topic and that is staffing and commitment generally. I think that what we are going to see when we go to the agencies is that this effort is feeling the pinch just like all other efforts within the agencies and it would be interesting to ascertain just how that pinch is being applied within the agencies.

Another problem that struck me as we went through the reports was the extent to which the exceptions that are contained in the Common Rule are being applied, particularly the exceptions for certain kinds of behavioral research, survey research and questionnaires. There does seem to be an unevenness. Perhaps even in some of the agencies a lack of sophistication or look differently. Maybe a feeling that those exceptions are broader than perhaps were intended.

Then the last concern that jumped out at me was the extent to which the agencies are on their own, fulfilling their obligations to obtain assurances from all of the entities, and here that becomes a -- I become aware of that not from just reading the reports but from my own individual questioning and sources.

So --

DR. CHILDRESS: Do you want to make that clearer?

DR. MANGEL: Yes, sure. I am sorry. Each agency that either regulates or assists research is to get assurances from the entities

conducting research or the entities that are regulated that they will comply with the requirements of the general rule. Now those requirements, among other things, would require the establishment of an IRB. They would require a commitment to a consent that is very well defined. They would require a commitment to a code of ethics. So there should be an assurance in place from each entity that is doing this before the federal agency assists or the federal agencies involved in regulating that.

MR. DOMMEL: Right. That is a detailed document, not just a signature on a line.

DR. MANGEL: Yes. It is a detailed and formal and described and supposed to be in place either in the agency or in certain circumstances the agency can rely on a general assurance that is in the files at the Office of Protection from Research Risk.

I think that that is an area where we should look. Once again I say this in the nonaccusatory way. I do not know what we are going to find. These are concerns that I think need to be looked at.

Now one of the things we have done is we have recently attended the most recent meeting of the Interagency Advisory Council and Emily was in attendance there. I am going to ask Emily to relate to you what we learned and saw there.

Emily?

DR. FEINSTEIN: Good morning. Well, as you know, the Human Subjects Research Subcommittee is an interagency group established by the Committee on Health, Safety and Food of the National Science and Technology Council.

Representatives from 17 federal agencies that adhere to the

Common Rule meet frequently to discuss shared concerns and issues and to oversee the implementation of the Common Rule. The chairman, Dr. Gary Ellis, spoke at our inaugural meeting.

In November NBAC sent a letter to several federal agencies requesting that they designate a representative who has the ability to discuss the agency's own implementation of the Common Rule. Now those responses are coming back in and the names are almost in every case the name of the representative on the Interagency Subcommittee, which is as we expected.

On December 11th, Bill Dommel, Joel Mangel and myself, we were present at the subcommittee meeting. We described briefly the work of the National Bioethics Committee and then the work that we have just begun with these interviews. During the course of the meeting the group raised several concerns that I think are relevant to the work of this commission, and I am sure that there are many others and Subcommittee and NBAC will probably continue to benefit from exchanging ideas in the future.

Of these relevant discussions is the possibility of distinguishing between biomedical research and survey research for IRB review purposes. The medical model is most often evoked when talking about research and the review procedure as it stands today serves us fairly well. However, it seems that non-invasive and non-risk research, including surveys, might justify a modified version of the present process.

Several members mentioned frequently the problem of over regulation. This is to some extent a corollary of the first issue regarding medical versus nonmedical research but it leads more directly to the

question of expedited review. Can expedited review be effectively implemented to maximize time spent reviewing higher risk proposals and minimize time spent on non-risk investigation?

Another issue that requires distinguishing is whether the Common Rule might be better enhanced in some way to fit the diversity of projects that need to be covered. The subcommittee is committed to maintaining that one Common Rule amongst all federal agencies. But at the meeting it was suggested that this rule might not be flexible enough or extend far enough to allow for the distinct objectives that each agency faces.

Lastly, the exemption procedure is one that may be not be understood or applied inconsistently. It may seem like the gatekeeper of this IRB process is not functioning up to par. The question of what exactly constitutes human subjects research and who decides which projects require IRB review arises frequently. The answer could be standardized in such a fashion as to eliminate much uncertainty.

Also several people raised concerns regarding the completeness of information gathered solely from agency representatives. Such individuals may not have as much hands on experience in the area of human subjects protection as others working with them. It is possible that persons who may have suggestions or experience in practical problems in their work with the application of the Common Rule will not be heard.

We intend to proceed in such a way that assures we are getting enough data from the right people. Undoubtedly doing so will require us to conduct additional interviews within each agency.

DR. MANGEL: That is pretty much where we are now and

the question then is what do we do next. Number one on our list, of course, is to hire someone or contract with someone to lead this project because I have been sort of holding back actually meeting with agencies until we have been able to do that because it seems to me that it would be critical to have the lead person on board before we actually started that.

Now we have taken some initial steps. We have sent letters to each of the agencies asking them to identify who it is in the agency that would be responsible and with an eye towards meeting with those people. Because I think that that is an unavoidable next step, and that is a series of meetings with the individual agencies to go over their responses and then to raise the concerns that we have and push on. I would guess that it is going to take more than one meeting with each agency. So there may be a series of meetings but at least one meeting.

In that process, as Emily has noted, I think we want to be careful that we are talking to the people who are the people in charge and that we have enough input from each of the agencies that we feel comfortable with the responses we are getting.

I think that not only can we find out from the agencies what is going on but they have got five years worth of experience that they can share with us and I think that is important that our approach to the agencies take on that kind of a tone.

So that is really what we have got to report and we turn to you folks to see what you think of all of this and what you would like us to do about it.

Bill?

MR. DOMMEL: I would just add that we have a couple of

target dates that Chairman Shapiro requested that an interim report, something very similar to what you have just heard here, be presented to the entire commission at its January meeting and that there be a report on the evaluation of the federal agency reports to the commission at its March meeting.

Now those dates were set with the assumption that we would have three to four people working on this project by the beginning of January and we may not make that and that date may have to slip.

PROF. CHARO: I am sorry, Bill. I did not quite understand. The March meeting that Hal Shapiro asked for a report on. Exactly what report did he ask for?

MR. DOMMEL: The report that Joel was talking about.

PROF. CHARO: Following the interviews.

MR. DOMMEL: Following the interviews.

PROF. CHARO: Following the interviews?

DR. MANGEL: Yes, the final report. Yes.

MS. FLYNN: May I ask a question?

DR. CHILDRESS: Yes.

MS. FLYNN: You will see that I will do this regularly, I am not a general participant in this arena all the time so I am -- I will seek a learning curve. But if you could, can you say a little bit more about what the current practice is and what some of the concerns were around the issues of nonmedical survey research and could you also add a little bit more to the comment you made about concern that there seems to be a misunderstanding or perhaps misuse of the exceptions?

DR. MANGEL: Sure. Those are very related. The answer to

both of those questions is very related. Stop me if I am going too far back on your learning curve.

But what the Common Rule does is it sets out a very broad statement of what is covered as is included in its terms and then sets forth a series of exceptions. Among those exceptions are things like survey research and questionnaires in which -- but it is not just all survey research. It is got to be survey research that is not risky and in which the respondents are anonymous in effect. Nonidentity. It is a nonidentifiable forum.

I get a sense that some of the federal agencies are applying that exception to what they are -- the things they are doing more broadly than others and possibly more broadly than a reasonable interpretation would -- each time I say this I want to add the admonition that I do not have any evidence to that. It is just -- this is my sense in reading some of the responses and my sense based on having been in the area for a long time.

MR. DOMMEL: That is the area you are interested in finding out about, right?

DR. MANGEL: That is one of the areas, yes. Just how they are applying many of the exceptions. Another exception is to certain -- is a feeling somehow and I think this comes out in Emily's report that what this regulation is about exclusively is medical research, and that some of the behavioral research may not be getting the kind of scrutiny that it should at least under the rules that exist today. Now that raises another question and that is, is that a good idea that the general rule be as broad as it is applied to all the agencies?

MS. FLYNN: Thank you.

MR. DOMMEL: I might add that these exceptions that are called exemptions precisely in the regulation, if you are conducting surveys and you are not going to record the identity of the individual or anything that could connect to the individual then, indeed, those are exempt with adults. And then if you are going to record it then you have a risk test relative to if the information became known.

Then the second major category of exemption, I think, that is used is the one for specimens and that are retained without identifiers or with identifiers, but if used in research without those identifiers then they are exempt from the regulations.

There is some confusion on that one. That is the big one for confusion because if you take the specimen away from its identifier but include something that might connect you to that identifier then that is not as we interpret the regulation that would not be exempt as long as it carried forward anything that could be linked back by someone.

DR. MANGEL: Another exemption, for example, that is now done by some of the federal agencies is the exemption that talks about public benefit programs that are conducted by federal agencies. I am telling you roughly what the exemption states. That was a very controversial exemption when it was first introduced.

It did not come along with the original package and it was put in place to allow for agencies such as the Social Security Administration, the Health Care Financing Administration, when they wanted to do some kinds of rent -- to examine some sort of rent subsidy programs. That is a tough one to apply and I think it would bear some

review by us as the agencies are applying it.

PROF. CHARO: More clarification also on the setting. Personally I am familiar with the IRB process and the review process at the level of the local institutions. But within agencies I am not familiar with it except to the extent that it comes up indirectly with the study groups at NIH. So I am still working by inference in exactly how these issues arise within agencies. For example, I gather that one context is with regard to purely intramural research that the agencies are doing, their own staff, exclusively their own funding, and on their own initiative. And the question is, is there anybody or how is anybody there monitoring this standard?

To what extent are you also talking about extramural research and agencies unlike the health related agencies that have the deepest expertise and to what extent are you talking about situations of collaborative research among agencies? Just to help me get a better idea of kind of the institutional setting in which these issues are arising.

DR. MANGEL: I am talking about all of the above. In other words, the responsibility is the same on the federal agency whether it is doing intramural research or whether it is supporting -- obviously it is not exactly the same. But I mean the same sets of rules apply. If it is extramural and the responsibility for having the IRB is on the institution doing the research. If it is intramural of course then the responsibility for having the IRB is on the agency. But the rules are essentially the same. So what I am talking about in all of these cases applies to both.

Now you raise an interesting issue because as I read through some of the responses I get the sense that the agencies are not always aware that those responsibilities apply in both cases and that is

something that we would probably want to look into.

PROF. CHARO: And is interagency research something that is a phenomenon to be considered?

DR. MANGEL: Interagency research?

PROF. CHARO: Yes. Or collaborative research across agency lines. Is that something that we need to be concerned with or is that nonexistent or so rare it is not really worth thinking about?

DR. MANGEL: Well, it is not nonexistent or rare because I know that, for example, NIH has got lots of collaborative projects with some of the other -- with other federal agencies. But they would be subject to the rule and they would have to comply.

Now what they could do is they could have a common institutional review board and one or the other's institutional review board could review the project but there would have to be an acceptable institutional review board in place.

PROF. CHARO: Is there a kind of understood or documented set of guidelines on how to do that? I ask because the phenomenon of collaborative and multicenter research out in the extramural world has been challenging the implementation of a lot of the regs that we now have and I guess I am wondering to what extent there is a parallel within the government with its own special governmental twist, but nonetheless a parallel phenomenon that might be suffering from the same confusion.

DR. MANGEL: Well, actually, I mean, I think I know the answer to that question, but Gary Ellis is here and Gary is the world's foremost authority.

How do you like that introduction?

DR. ELLIS: (Not at microphone.) The rule attaches to federal funds from the 17 agencies that are committed to the rule -- My name is Gary Ellis, Director of the Office for Protection from Research Risks.

The rule attaches to federal funds that flow from any of the 17 agencies that is committed to the rule whether it is intramural or extramural. You have asked about a specific case where there is intramural collaborations between or among agencies. And I can answer to the extent that our office would ever be involved if HHS funds are being teamed up with another agency.

We look to the performance side of the research and make sure that it is an assured site in one way or another, and that an IRB is named and is cognizant that there is the same sort of governance as you would see in the extramural community. Sometimes political relations between or among agencies make that problematic but we try and iron it out.

PROF. CHARO: But how would that come to your attention?

DR. ELLIS: Well, we heard Emily attended the Interagency Human Subjects meeting last Wednesday and we heard about NIOSH, an entity within the Centers for Disease Control and Prevention, working with the Department of Energy, and I see Dr. Susan Rose from the Department of Energy is here, and so that is a case where an HHS entity and the DOE entity need to work together. I know that our office was involved in meeting with the parties in deciding exactly who was in charge and what the governance would be. So that is an ad hoc response to a particular case.

PROF. CHARO: One last -- I am sorry for pursuing it, but I just really -- it is like I think best when I can think very concretely. But if I understand correctly nobody is obligated to notify OPRR that they are about to embark on this kind of research.

DR. ELLIS: That is correct.

PROF. CHARO: So if NIOSH and DOE had decided to do this and had gone forth to research they would not necessarily have to consult with you. I guess what I am wondering is how clear is it to people at NIOSH and DOE, to take two examples, of how to proceed now in terms of collaborative design and review and monitoring of the protocol for compliance with the Common Rule? Is it an ad hoc arrangement each time or is there kind of a regularized way of going about this? That is, I guess, the essence of the question.

DR. ELLIS: There is no office in the federal government that is a central authority that has authority over all human subjects research across the federal government. Each agency is responsible for its own funds. OPRR in the Department of Health and Human Services could be described as first among equals because of the assurance process. So if there is an assurance with the Department of Health and Human Services in place at a research site that must be deferred to by other agencies. That is in the Common Rule.

PROF. CHARO: I see. So that the site itself through its assurance will be the one who controls how it is that they are going to implement the --

DR. ELLIS: That is right.

PROF. CHARO: Thank you. Okay.

DR. ELLIS: In your specific example OPRR would have been involved because NIOSH is an entity within the Department of Health and Human Services.

PROF. CHARO: Okay.

DR. ELLIS: But let me pursue it. If two agencies other than the Department of Health and Human Services were involved there certainly is no requirement that OPRR be notified about research they may be collaborating on. Although if it is occurring at a site that is assured by the Department of Health and Human Services we would be involved.

PROF. CHARO: Okay. Thank you.

DR. CASSELL: Maybe as long as you are sitting here, how often does it happen that a complaint about -- in the particular research -- piece of research you get complaints about the way that subjects are being treated? How often does that happen?

DR. ELLIS: Well, I can give you an absolute number but I cannot give you a rate. In other words, I can give you the numerator. We have at any time about 70 investigations of a noncompliance act in a given month. That is a numerator. I do not know how to express the denominator. I do not know how many human subjects there are involved in research. I know perhaps how many sites are involved.

DR. CASSELL: Leaving out the numerator for a moment -- I mean, the numerator is quite impressive. So why is it -- tell us a little bit about that if you would. How they get to you? Why did they get to you and so forth.

DR. ELLIS: About half of the complaints that reach our office come from the institutions themselves. So you can describe these as

self-reports. The other half are a combination of reports from press, Congress, aggrieved individuals, institutional review board members. You could use the term "whistleblowers." We have complaints of that nature where the subject absolutely does not want to be identified but has information that he or she considers important. So we try and receive with a -- with a net everything that comes our way.

PROF. CHARO: But this is not now agency stuff, you are talking about across all institutions?

DR. ELLIS: About -- I was going to say about one-fifth to one-quarter of those complaints are research that is not funded by the federal government.

DR. _____: (Not at microphone.) I think it is a little higher now.

DR. ELLIS: A little higher.

DR. _____: (Not at microphone.) As much as thirty percent.

DR. ELLIS: As much as thirty percent of the -- as many as thirty percent of the complaints we get are about research not funded by a federal entity which is a sobering fact in terms of our authority and our jurisdiction because our authority with certain exceptions stops where federal funds stop.

So we are talking about the perimeter of protection of Americans who may be -- for Americans who may be involved in human subject research, the protections of institutional review board review, of informed consent. There is a perimeter of that protection and there are individuals who are human subjects in the United States who are beyond

that perimeter today.

DR. CHILDRESS: We are going to come to that later today too. So I do not know how far you want to pursue it --

(Simultaneous discussion.)

DR. CHILDRESS: -- wrap up in the discussion of what is happening in the agency review.

Any other questions, comments, directions?

PROF. CHARO: One other -- I am sorry, Jim.

DR. CHILDRESS: No, I have some too.

PROF. CHARO: You mentioned that -- where is my list of questions? Here it is.

You mentioned the problems with staffing and I guess implementation. I guess I am wondering about two things. One is going to connect to the national coverage, so please just keep in mind to which national coverage might simplify some of the questions about assurances that are being negotiated with individuals, et cetera.

But for the point here, what available resources are there for essentially allowing self-training about what is or is not an appropriate interpretation or implementation of the regs? The only things I know about that are the OPRR reports, the IRB, the Blue Journal, IRB, and a private informal discussion list run through Medical College of Wisconsin on IRB's. But is there anything else by way of kind of data bases that let people --

DR. MANGEL: Okay. When you said resources I thought of dollars, but you are talking about -- I do not know. I would have to find out.

PROF. CHARO: Okay. Thanks.

DR. MANGEL: Each of the agencies is supposed to be doing

education within the agency.

PROF. CHARO: Right.

DR. MANGEL: And that is something that we would look at. But in terms of what kinds of resources are out there, I do not know.

PROF. CHARO: Okay. Thanks.

DR. CHILDRESS: I can distinguish two kinds of problems. One would be problems that you are observing impressionistically so far and have not yet been able to put into sharp focus until you can really talk to more people. Distinguish those problems that you observed from felt problems, the problems with your report group working on this, and you suggested that some of those had to do mainly with concern about the over regulation.

Are there any other kinds of things emerging from within the reports you are getting about where people find problems or find gaps, vagueness, or any of those kinds of problems emerging to you?

DR. MANGEL: Emily, did you hear of anything that --

DR. FEINSTEIN: Well, the list that I reported to you were things that I observed at the Human Subjects Research Subcommittee meeting. We have not done enough actual work going out and conducting these interviews to answer that and certainly besides that many of the people have not been contacted and asked. That is what we are hoping to find in the coming months.

DR. MANGEL: I think that one of the problems that we are going to really discover is the result of the diminishing resources that are available and what happens is then that agency's attention goes elsewhere so that while you have got some people in place, you will have many people

in place, and maybe the people in place are not any longer in the line of information that would enable them to do their jobs. I have a feeling that that is something that we are going to find out about.

DR. CHILDRESS: You mentioned at the very outset, and I do not think we are returning to it, that Executive Order does require each report to contain an identification of the measures that the department or agency plans or proposes to implement to enhance human subject protections. Are you finding a lot emerging in terms of the enhancement side?

DR. MANGEL: No, in words of one syllable. One thing that is interesting is that the report -- the required -- the Executive Order and its requirements itself seemed to have stirred up some activity so that the reports do indicate that there is currently in the works policies which seem to date from about the time they would have gotten the request for the report. So there is that kind of thing in the works.

MR. DOMMEL: But that is expressed in the same kind of unevenness, I think, that you --

DR. MANGEL: Oh, yes.

MR. DOMMEL: That is another point.

DR. CHILDRESS: One more very practical question, when we are identifying people to talk to and so forth, are you finding that any of the leg work done by the advisory committee useful since, I think, the advisory committee on Radiation Experiments actually spent a lot of time on this as well and in some ways this particular requirement is an outgrowth of that.

DR. MANGEL: Yes. Yes, they have been helpful in

forwarding information, the names and information on people, and they have been a resource from when we asked about particular people.

DR. CHILDRESS: Other questions, comments? What kinds of direction do you want to offer?

DR. CASSELL: Well, I -- what interests me particularly is turning around somewhat. There are problems in getting -- in doing research that human subjects raise. I understand the protection of human subjects and the need to have human subjects, the whole thing. A lot of the things that go on and the abuses are the attempt to get human subjects because it is really very difficult where people would not otherwise consent or it is hard to get the survey done if you follow the rules and so forth.

I am sort of interested in this difficulty of doing research that the regulations propose in order that -- I mean, I have an underlying reason for it, it is to find those loopholes where people are trying to find a way. People try to find a way out when they are trying to get something done and they cannot get it done because the regulation gets in the way.

There are two solutions to that. One of them is to point out -- one way or another point out what then needs to be done. The other is to find another solution for it. But both of them are educational functions. I mean, they are not just regulatory functions. But I am interested if there is some way we can find out what trouble we have got and how that trouble has specifically impacted on the work of an agency or agencies that exist underneath an overriding body.

DR. MANGEL: Well, we have got -- we have got 16 agencies that will have five years worth of experience and that I think should be a

real focus of our inquiry. I mean, I do not think this should be exclusively an inquiry as to where are the bodies, you know. It is what are the problems and what are your suggestions. We have already -- we have been hearing some of them. I mean, expedited review is a suggestion that we have heard and we continue to hear as, for example, addressing the terrible work load that the IRB's have.

DR. CASSELL: I am also interested in what kinds of research are not in the perception of the agencies or the organizations under them is not getting done or is getting done but with great difficulty or was compromised in its quality or whatever. And, in effect, to get underneath the regulatory, you know, answering questions on a regulatory questionnaire.

DR. MANGEL: You mean can you really have a good double blind study without running afoul of some of the ethical considerations?

DR. CASSELL: Yes, there are issues in which double blinding is very, very difficult. There may be -- I mean, Ed Jonas (?) would have said there are certain things that you will never know about. There are things you will never know because it is more important -- there some things are more important than knowledge. He also pointed out that it is very difficult to make that clear.

PROF. CHARO: I think other areas where Eric is talking about might -- other areas of research that might raise exactly this point because this is very good. Situations in which there is a standard therapy and the difficulty is in testing whether or not the standard therapy works. I am thinking specifically now about vaccine development which to some extent has moved outside the U.S. I know into Sweden, for example, in

part because of the difficulty figuring out a way to design a protocol that met current notions of what is an acceptable set of choices.

I think that the interpretation of minimal risk or just a minor addition of risk beyond minimal risk is another area that I suspect that there is a lot of gamesmanship going on in order to accommodate research that otherwise would not be done because its risk/benefit ratio for the particular subject is unacceptable and that subject falls in a vulnerable population category of children and so there is an effort to find some way around that through creative interpretations of minimal risk.

The last part of the list, the research in the emergency context, which was just worked on by FDA raised exactly these questions too. I think that is actually a very good point because if you fill a box with water it will creep out of every crack and it would be very interesting to find out exactly how it is creeping and maybe find a way to come up with a more realistic set of regulations. That also accommodates realistic assessments of what is acceptable.

DR. CASSELL: There is a recent argument in the pages in the New England Journal about the use of angioplasty, balloon angioplasty versus pharmalytic therapy in the treatment of acute myocardial infarction. One of the commentators said he could not conceive of any -- he could not conceive of an angioplasty person, people who do that, participating in research which compared the two anymore because they would feel it was unethical they are so sure that they are right.

Well, by being so sure that they are right that stomachs got frozen numbers of years ago in the treatment of bleeding and a number of other things like that where it simply -- they just simply do not understand

and consequently research does not get -- or they simply do not understand and research does get done. And that could be picked up by people who are overseeing this. That is something that a nonangioplasty person picks up very quickly. Now you may be so sure but the rest of us are not quite so sure. Agencies must pick that kind of thing up and you have a space -- you know, conversation in the room instead of getting out of the room.

PROF. CHARO: Eric, do you have any idea how you would begin to get at this kind of information? This is a tough one because this is not about the agencies. This is about the individual researchers and how they put together their protocol and the IRB's they are operating within the agencies and how --

DR. CASSELL: Well, it is the same thing as the problem about the IRB. The IRB's -- has anybody done a good survey where IRB's get -- in some method that gives us enough data to know what they think their problems are, what is getting through them, and where they are throwing up their hands. I mean, all of us probably have been on IRB's at one time or another. There are things that you just throw up your hands because it is too difficult or stop it because you cannot figure out a way around it even when you know the research probably should be done, but you cannot figure a way around the protection and so you stop it.

I am interested in that level of understanding of what IRB's do and I know that it poses problems because it is -- you are not going to get that in the answer to a questionnaire. That is the kind of open ended question research which is very important. I mean, we are well into this enterprise now, well enough into it so that we begin to need a kind of data we have not had up to now.

PROF. CHARO: Well, that is exactly what Dave ought to go out and do, is interviews. The question is who would you suggest he interviewed to make sure that what they are thinking about and what we are thinking about are dovetailed and that they will be able to get the information you are hoping to get?

DR. CASSELL: Well, I do not know the regulatory structure well enough to answer the question above. But the IRB level I think IRB directors have to be interviewed. I think, for example, the nontechnical members of the IRB have to be interviewed. They are always ready to talk to you privately and they are always expressing frustration that they do not know what the hell is going on until they have been there two years. And by the time they have been there two years they are about to rotate off again. So another ignorant person is about to come on and get educated for two years.

DR. CHILDRESS: Part of what you are focusing on, I think, is very difficult to get at because you are, it seems to me, in part asking about tacit assumptions that probably will not even come out in response to specific questions. It is not simply the questionnaires, but even the responses to specific questions. It is the kind of thing that maybe anthropologist could get at following an IRB over time because there are several different layers of --

DR. CASSELL: Well, you know, those --

DR. CHILDRESS: -- understanding --

DR. CASSELL: -- we are perfectly free to propose research questions also.

DR. CHILDRESS: Right. We might come to some of that

particularly when we talk about the IRB's. I think in some unlimited budget we could develop to --

DR. CASSELL: Anthropologists are cheap.

DR. CHILDRESS: Okay. All right.

PROF. CHARO: That is true.

(Simultaneous discussion.)

DR. MANGEL: The way I envision this we will get some of that, but I do not think that we are going to be equipped to deal with that question definitively. I think that a lot of --

DR. CASSELL: We add enough of it so that we begin to know what is the question that we might be able to go at in greater depth.

DR. MANGEL: Well, I think that people at NIH and some of the other agencies are going to be able to tell you where the problems have been because they get applications in and they have to throw up their hands and so they know where they have been throwing up their hands. We can get some of that I would guess.

DR. CHILDRESS: Is that the guidance we wish to offer at this point?

PROF. CHARO: One other thing. In a sense it is difficult to discuss until we talk about things like national level coverage, but do you think it will be realistic in your work to try to get a handle on the difference in the work load having to do with kind of paper shuffling? In other words, the difference in the resources that might be paid out if we were to adopt any one of a number of possible kind of big level guidelines? Putting aside how would we legislatively authorize it. If there were protection for every human subject in the United States what difference might that make to the

work load of the agencies?

DR. MANGEL: When you say "protection" what do you mean?

PROF. CHARO: If, for example, we were to seriously discuss and maybe conclude that there ought to be some attempt to make federal law that requires that every entity doing research in the United States with human subjects is subject to some basic minimum set of regulatory protections that are in common.

One can imagine that that might change some of the implementation strategies now in place having to do with things like assurances, et cetera, and you had mentioned specifically that sometimes there is difficulty in implementing or following the paperwork on stuff like that. If we could get a handle at all on how much would be freed up by virtue of eliminating some of the extra paperwork and regulatory stuff that goes along with a more fragmented system it might be helpful in figuring out kind of a cost benefit analysis and pursuing new strategies.

DR. CASSELL: Oh, I follow you. In other words, if there was -- instead of having to apply them all over the place, if every single subject in research --

PROF. CHARO: Right.

DR. CASSELL: -- then that creates a guy whose sole job is that rather than having it in 27 different agencies.

PROF. CHARO: Exactly. Essentially what it would mean is that there is the possibility any place that wanted to do research on site has to have some kind of assurance filed with one entity. It does not have to work individually with every agency and there is registration data, et

cetera, et cetera.

I mean, there are a whole variety of things that we will discuss later. But that is why I said it is kind of hard to figure out in which order to discuss these things. But trying to get a handle on the amount of kind of wasted effort that is created by virtue of the fragmented coverage we now have, it would just be helpful figuring it out.

DR. MANGEL: Yes, I do not know the extent to which our inquiry could really get at that. Maybe Gary would be better to look into that issue.

DR. ELLIS: I think that the agency reports that Joel and the commission have in their possession begin to describe the effort that exists now but I think that he has already told you -- he did not use this word -- but some of the reports are quite crude. The agencies themselves do not even report very well what effort they have in place now or perhaps they have little effort and so that is why the report does not reflect it.

DR. MANGEL: I did not use that word.

DR. ELLIS: So I cannot really give an estimate of what effort exists across the federal government today. Now the Radiation Commission presented data on the number of personnel applied and I believe only two entities have full time personnel dedicated to human subject protections. Other agencies have portion of FTE's put together. So there are some estimates in the Radiation Commission report.

But to answer your question what would the effort necessary for a unified national system be, I do not have any estimate of that. Now there may be parallels found in the system protections that we have for laboratory animals in research where one agency, one secretary, has the

lead.

There is, as you described, a registration requirement and in the case of animals a requirement to report painful procedures, procedures where pain is ameliorated. So there may be parallels in the system protection which has been in place for 30 years since 1966.

PROF. CHARO: Thanks.

DR. BRITO: Could I ask Dr. Ellis something because this would help me a lot in terms of guiding where we are going? You had mentioned before you were working on 70 different projects at one time in terms of complaints or possible violations. Can you give us an idea of what the nature of those complaints are and which ones you find to be true violations? And what are the consequences to the investigators once you do find violations?

DR. ELLIS: Probably the most common element in the complaints are problems in the informed consent process. Ninety percent of the complaints will be problems of informed consent. We have authority to help institutions receiving HHS funds improve their process and the ultimate authority we have is to restrict or withdraw the assurance which would mean that those federal funds could not flow for human subject research. That is an authority that is very rarely used because it very rarely has to be used.

Almost all institutions once they recognize the problem or we help them recognize the problem are very much interested in fixing it and improving it. So we are able to effect change in that way through educational means. Sometimes education has to follow a problem and that is disappointing when the gain must follow pain. But that is what we do

day to day.

How many of the complaints ultimately have merit? That is not an estimate that I made previously. I am going to ask Tom Puglisi -- we just have not estimated that. What percentage of the complaints ultimately have merit?

DR. CASSELL: That is important, though, isn't it?

DR. ELLIS: Well --

DR. PUGLISI: Maybe I can address that.

DR. ELLIS: Introduce yourself.

DR. PUGLISI: I am Tom Puglisi. I am the director of the Division of Human Subject Protections in OPRR.

I would say that of the complaints that we receive and decide pursue, and understand that there is something of a filtering process in which we evaluate whether or not there may be a substantive question involved in the complaint. But generally when we pursue a complaint it is often the case that we find some problem either with the informed consent process or the record keeping.

So I guess on one level I could say that a fair number, maybe half or more, of the incidents that we investigator do have some legitimate substantive complaint that requires some corrective action. Often the institution will have on its own identified the problem and propose a corrective action. Sometimes we will have to propose corrective actions. We will also look at an institution's system of protections and often find flaws in the system that we recommend protections for.

On the other hand it is relatively infrequent for us to impose a restriction either limiting the scope of an assurance or requiring

corrective actions on a specified time table. We probably have about eight to ten institutions right now that are operating under restrictive assurances and the typical scenario there is for us to identify a series of rather substantive corrective actions that have to be implemented over a specified period of time according to a specified time table.

We very rarely take any action against a specific individual investigator. We are interested mostly in looking at an institution's system of protections and we review individual complaints as reflecting laws in the institutional system of protections.

We could if we found a particularly egregious action by an individual investigator recommend debarment to the HHS debarring official. But that would be an exceedingly rare event.

DR. CASSELL: Has it ever happened?

DR. PUGLISI: My understanding is that there was one case in which OPRR was about to consider recommending debarment and there was -- the investigator voluntarily --

DR. CASSELL: Killed himself.

DR. PUGLISI: -- voluntarily pledged not to engage in HHS supported research.

DR. MANGEL: But there is another mechanism within the department for addressing scientific integrity.

DR. PUGLISI: That is right. Scientific integrity is a different process that is governed by the Office of Research Integrity. We have a good working relationship with ORI so that if they identify research integrity problems that have a human subject component they notify us and vice versa, and we will conduct parallel investigations. We also have

connections with the compliance offices in the FDA, Centers of Drugs, Devices and Biologics, so that we share information that way as well.

DR. MANGEL: And they have debarred people?

DR. PUGLISI: Right.

DR. CHILDRESS: Okay. Other points you want to make for staff for doing this mandated project?

I think we might summarize by saying continue and obviously some of the questions that have come up involve matters of trying to get at some of the issues as deeply as possible and we know that is difficult. We will look forward to getting further response in actually just a few weeks. So it may not be terribly different at that point than today. But we appreciate your efforts.

Anything else to add?

We had everyone introduce themselves about an hour-and-a-half ago. Could those that have come in since that period who did not introduce themselves please do so, just give name and where you are located, and institutional affiliation.

DR. _____: (Not at microphone.) (Inaudible).

DR. CHILDRESS: Let's go around.

DR. _____: (Not at microphone.) I was here.

DR. CHILDRESS: Okay.

DR. SOBEL: I am Mark Sobel, National Cancer Institute.

DR. PRITCHARD: I am Ira Pritchard from the U.S. Department of Education.

DR. _____: (Not at microphone.) I am Pam (inaudible).

DR. CHILDRESS: Anyone else in the row here?

DR. PETERS: Judith Peters, National Center for Human Genome Research.

DR. STOKLOSA: (Not at microphone.) I am Janice Stoklosa, NASA headquarters.

DR. _____: (Not at microphone.) I am Joan (inaudible).

DR. LAWSON: Becky Lawson, NIH.

DR. ROSE: Susan Rose, Department of Energy.

DR. FOLGER: Ruth Folger, Uniform Services University.

DR. _____: (Not at microphone.) (Inaudible).

DR. _____: (Not at microphone.) (Inaudible), FDA.

DR. SUTTON: I am Jennifer Sutton from the Association of American Medical Colleges.

DR. _____: (Not at microphone.) (Inaudible).

DR. CHILDRESS: All right. Thanks.

All right. If we can hold up without a break at this point, are the subcommittee members okay to continue?

DR. CASSELL: Yes.

CHANGING PARADIGMS AND PRINCIPLES OF RESEARCH WITH HUMAN SUBJECTS

DR. CHILDRESS: Let's turn to the topic of changing paradigms and principles of research with human subjects. Some points along these lines came out in our subcommittee members' initial presentations. The central question is what has changed since the work of the national commission which was referred to earlier.

What has changed in the research enterprise? What has changed socially? What has changed in our understanding of the principles

that are relevant to research involving human subjects? What sorts of changes have occurred that would require us now to rethink, to modify, to alter, to restate the kinds of considerations that were operative before?

So that is a kind of background comment. I have asked subcommittee members to kick off different portions of our discussion of these topics. Alta Charo, who raised this in one of our e-mail exchanges, will kick this part of the discussion off.

PROF. CHARO: Because obviously I do not talk enough as it is. Thank you very much.

DR. CASSELL: You have got the fastest fingers in the world. I have figured that out.

PROF. CHARO: That is why there are so many typos.

I asked this question truly in the spirit of asking and you saw the materials by Carol Levine, I think, which was the very first set, particularly no written presentation. She is a pleasure to read, isn't she? Presentation of one possible change in kind of underlying assumptions that drive all the rest of the world's human subjects research. That has to do with whether research is a threat or a benefit to the subjects who are enrolled.

As she notes, the whole set of rules was something that grew out of a variety of horrendous experiences in which research subjects were tremendously misused and abused. So all the regulations are written from the point of view of protecting subjects from abuse. The emphasis is on substantively when you have gone too far in terms of exposing people to risk and in terms of documenting the degree to which they are voluntarily and informatively exposing themselves to whatever risk has been

subsequently approved as within tolerable range.

But recently the American public and the research community have been struck by two conflicting tendencies. One is a continuation of that notion of research subjects as vulnerable and I think the Radiation Commission reports, although they were talking about experiments long ago, raised that again in people's minds in a very dramatic way.

At the same time probably most notably with activists surrounding the AIDS community there has developed the notion that some types of research represent potential benefits and I think that this is going hand in hand along with perceptions of frustration at the speed with which new drugs and devices are developed and approved by FDA and introduced into the population. So that there are specific groups that have seen lack of access to either investigatory drugs and devices or lack of access into clinical trials as a denial of a potential benefit.

The other large groups that fall into that category, I think, are primarily women for whom there has been a lot of discussion of inclusion of women, particularly women of fertile age.

And, in addition -- and this is kind of a little different, rather than a kind of exclusionary paradigm in which you want to exclude as many people as possible because they are potentially victims or the inclusionary paradigm, which you want to let people in because it is a potential benefit, there is the kind of partnership paradigm.

And I think that this is coming out of the gay community in which research surrounding things like genetic phenomenon that will or will not make people more or less likely to act on homoerotic impulses has

generated tremendous dissention within that community about the wisdom of the research because they can see all of its implications for how it would play out in terms of legal decisions and social responses.

And in light of these changed experiences and in light of the fact that I, frankly, do not have a good handle on the sort of relative proportions of research that would be if we were to grossly classify potentially abusive, potentially beneficial, and potentially in need of more of a partnership discussion. I am interested in thinking through whether anything about the underlying paradigm of the current regs is worth changing and, if so, how it could be done because it may be that the implementation is a cure that is worse than the disease.

Then bound to these things finally is simply running through this whether or not the key distinctions are still the same. For example, we do not distinguish in the current set of regs between publicly and privately financed. More particularly publicly or nonprofit financing versus for profit company financed research at institutions that have multiple assurances. Since the private sector's use of hospitals and medical schools as a site to do their research has increased dramatically I do not know if that is now a significant factor driving what kind of research it is, the likelihood of risk/benefit balances, the importance of the research and the way we ought to respond from a paradigmatic way.

So really I do not know that the current division is between biomedical and survey or human and nonhuman animal research are as valid as they used to be now in the era of xenotransplant.

So I find all these things kind of on the table just to kind of want to clear away the undergrowth of what direction the regs ought to be

taking. So probably the biggest one has to do with the underlying kind of exclusionary, inclusionary or partnership tacit understanding that underlies the regs with the other issues being drawn in as appropriate.

I do not know if people have instincts about where this ought to go or what research is needed to know where it ought to go or whether it ought to just stay the same.

DR. CASSELL: Well, I mean in a way the whole idea of a research versus the subject, which was the original picture and which is the picture reemphasized by Ruth Baden's report, is that it is like -- that there is a necessary adversary relationship between whatever the researcher wants is not in the subject's best interest and, therefore, we protect the subject from the best interest of the researcher because they do not coincide. That just does not a fit a lot of research that is being done now.

The whole idea that what society gets out of research now as opposed to the idea of what it did before. But the picture of science in 1990's and the picture of science in the 1960's are as different as one could conceive of. And yet -- so to some degree what people know about the AIDS -- yes, she does, she writes beautifully because she started off as a writer and editor, that is why.

Anyway to some degree what you report in the gay community and people with AIDS, and we could find other inheritable diseases where there is a very close connection between the people who do the research and the people who are the recipients of it, benefit and who are the subjects of the research. Particularly in small diseases or small not in what they do to people but in the numbers --

PROF. CHARO: Orphan diseases.

DR. CASSELL: Orphan diseases, right. And so that has all changed and yet the regulations do not really reflect that. The question is whether in the nonregulatory part of the research establishment that change is reflected and in the behavior of individual researchers, and the education of scientists. That is the question that is in my mind. That is the change in the education of science that has happened as these changes have taken place because they know their relationship to their subjects has changed.

DR. CHILDRESS: And sort of to go back to the work of the national commission, so much of that discussion focused, for example, in children on nontherapeutic research versus therapeutic. Part of the shift you are talking about is really a shift away from a focus on the nontherapeutic. To set up the regulations to deal primarily with that and then we add the therapeutic or whether we are also are maybe primarily concentrating on the latter now. I realize that distinction is not a hard and fast one, but still if one looks back at the literature, looks back at the discussion, there is so much of it with prisoners and with children in particular focused on the nontherapeutic.

I guess, again thinking of a kind of shift that may be reflected in this, some of the points that both of you have made perhaps would suggest as Carol Levine's article does too, and other materials as well, that maybe we are now having to give increased attention to the issues of justice if we take the three principles of Belmont of respect for persons and beneficence, and justice.

Particular attention to justice requiring a kind of participation on the part of various parties in setting research design and

the like, determining research priorities on the one hand. But also justice in the sense of access to promising therapeutic procedures that are available only in clinical trials.

Those two aspects of justice have received a lot more attention. Not that -- as we make several of these points, not that we necessarily go back and revise the regulations seriously, but we may well conclude certain kinds of things that were not given enough attention before. At any rate that may be one of the results of the shift.

MS. FLYNN: I was pleased to hear your comments and I think they are very important in terms of the relationships that are in place or growing and changing our understanding of partnerships that we would like to see between the research and scientific community and research subjects.

But I do not think we are fully there yet. At least it is my sense that we still lack sufficient emphasis in medical and scientific education, a basic working knowledge of ethical decision making. I have been surprised in just asking in various medical and research meetings this question at how few individuals have actually had even one course during their education or even post their graduation that really focuses on these issues even though we know they have become much more complex and more highly regulated.

I also sense much to my surprise actually a fair degree of resistance in at least the upper reaches of the medical and research establishment to the notions of partnership that many of us would like to see where there is a full participation in research design, where there is some real effort to consult early with the subject community, the disease

entity and its interest groups and so on, to get at the issues and questions that are of concern to them, to more fully explicate some of the procedures and their utility. I think there is a lot of head nodding that goes on around this. But I do not frankly pick up a great deal of resonance to it in places where I would like to see it.

So it seems to me that we might -- using this commission's deliberations -- have an opportunity to further that notion and offer some specifics as to how it might begin to be implemented. There certainly are those who embrace it. But I think that the research and medical establishment, in general, is not comfortable. They have proven to be uncomfortable as the AIDS community has moved forward and I do not think that that experience has necessarily given them a great deal of ease with the subject of engaging in partnership, in a true partnership fashion, with various interest groups of the community that represent the community subjects.

DR. CASSELL: Don't you think, in part, that the -- that the -- when you say the higher up you go the resistance is greater, you are also going up the age span spectrum where younger investigators have no experience with being -- that is too strong perhaps. But the idea of partnership is just not there. They have a thing they are doing and here are their subjects and so forth. So that part of it is the difference in the attitude of different age -- in different age groups.

MS. FLYNN: I think that is --

DR. CASSELL: And if you say the word "education" about every ten minutes, you said, "Education," until we all said, "Well, education. There is something that we might have something to do with." Well, that

would be wonderful.

MS. FLYNN: That is true. The age issue is real. I think there is also a continuing undercurrent of concern about resources. At the practical level the more that we add additional, however valuable, and I would think this to be a valuable one, additional requirements or additional levels of consultation and participation, that the more that becomes seen as a hurdle and the more resistance there is to what is already seen as a very difficult process of getting through the research.

DR. CHILDRESS: Are there other shifts that are important for us to keep in mind?

PROF. CHARO: I think that there are others. I think that the public-private one is probably worth some more discussion perhaps because of the possibilities for slicing research and the degree of review either based on substantive issues like perceptions of the risk/benefit or more kind of procedural grounds like who is sponsoring it, which may turn out to be a fairly good proxy and easier to implement.

But before we get to that inclusionary/exclusionary type stuff -- I do not even know what I think about this. I am really curious about what people think about this. On the one hand because I have -- I have written on the problem of access to research from the point of view of women and worked closely with somebody who was a scholar on the history of the enrollment of minorities, particularly African-Americans in research.

I am familiar with the debates surrounding inclusion and research as potentially beneficial to the subject as well as the phenomenon of failure to think of the IRB's role not only in terms of excluding people

who are going to be abused, but also making sure people are included to benefit the larger society when the research is done. That I am comfortable with.

But after you watch the reactions to the Radiation Committee's investigation, first starting with Hazel O'Leary's announcement and then the investigation report, watched the degree of interest in writers in the New York Times and the Washington Post, and the people who read it, then the phenomenon of the Persian Gulf experience and the whole subtopic of the use of investigational prophylactics against chemical and biological warfare. My bottom line question is the following:

Is the problem of lack of access to clinical trials both for the people who think that they have benefit as well as for the greater good of the quality of the medicines and devices that emerge, is that issue large enough that it should be addressed despite the continuing concerns about abuses in research or is this still a time in which the need for public confidence and the need to actually crack down on abuses is so strong that you want to retain the current kind of paradigm of the vulnerable subjects and you want to retain the current focus almost exclusively on protection of subjects until such time that we are comfortable that we have really gotten a handle on that?

DR. CASSELL: Alta, do you think that there will ever be a time when people are comfortable that nobody is ever being abused as a subject and that nobody is ever being taken advantage of, and nobody is being recruited wrongly?

PROF. CHARO: No, I do not.

DR. CHILDRESS: How do you feel about human nature --

PROF. CHARO: Right.

DR. CHILDRESS: -- and some changing interest.

PROF. CHARO: No, I do not. But I do think that there comes a tipping point at which the threat that is posed by having anything less than an absolutist approach that focuses on protection of human subjects, there comes a point when that threat is not so great because we have really gotten a handle on protection of subjects, and then the lost benefits to individuals and to whole populations in terms of what emerges from research by virtue of failure to include begins to become important enough that we can now abandon the kind of absolutist right line approach and try to do a more nuanced regulatory take on research.

My question is kind of are we there now because we know the groups that want to be included or that need to be included have been making lots of noises and getting lots of attention. I just do not know yes or no whether this is the point at which to acknowledge that or whether there is still such a -- where the right line is going to be such a threat to -- is going to be so undermining to the effort to actually prevent abuses that we cannot afford to do it now even though we recognize it needs to be done.

DR. CHILDRESS: Arturo?

DR. BRITO: I think the same people or individuals and/or groups that are set up for abuse are also the same ones that are set up to be excluded. This is a generalization. But also could be set up to be excluded from clinical trials that could be beneficial. So the answer to the question is I think we do need to address it within the context of addressing the abuse issue.

DR. CHILDRESS: So your argument is that the two can be combined in ways that would not lead you necessarily to sacrifice the protectionist side?

DR. BRITO: Exactly. There are clinical trials that are beneficial to human subjects that do involve some risk but the benefits outweigh the risks and the same group of people who may be abused in one situation would tend to be excluded from those clinical trials.

PROF. CHARO: That is actually -- that is a very interesting observation because if you look at the mechanism by which people get excluded, one very common one is through a protectionist criteria. People are defined as vulnerable and then they are excluded because of their vulnerability, and then they do not have access. I mean, I called it protecting us to death when I was writing. That is very interesting because that actually does make the problem a little easier to deal with. It means that you refocus your attention on the definitions of vulnerability and what it implies instead of having to think about the kind of paradigm of research.

Are there any other groups that have been excluded that do not fall in this category and have been excluded for other reasons? I mean, I am just trying to double check my impressions.

DR. LEVINSON: Well, just as a sense -- you know, going back to resources. The AIDS community, people who are literally dying to get on a clinical trial, on a protocol, that started changing our definition of, for example, abuse. Abuse might be just simple exclusion, not what happens once you get in the protocol. That whole issue started changing a different paradigm, the regulatory paradigm.

One from where our country was extremely adverse and that

FDA was out there in order to protect against a single incident having to do with premature approval of a drug to one where people are trying to get access to drugs under investigational approvals, let's say, at an earlier stage in the development process than they had in the past. So that our paradigm in the regulatory sense has shifted and I would expect that, in fact, you might have seen the research paradigm shift first. It would have been more expected, I guess, to see that earlier.

I am particularly happy to see this particular issue on the agenda because it speaks to an important aspect of the establishment of NBAC, which was to be forward thinking, to look at trends like this and to see how our earlier models may have applied to a paradigm or picture of the relationship between the researcher and the patient or the subject. That has changed as our country changes and our public attitudes change in our attitude towards research and our attitude towards access.

I was interested in Gary's point about some of these complaints. There has been time enough in the past five years or so to see if there have been trends in the kinds of complaints. What do patients see as abuse? What do patients see as something legitimate to complain about? That may be changing and we should know whether or not that is changing.

Your point, Alta, about the Radiation Advisory Committee is very important. It has raised people's sensitivities towards the past definition of abuse and we may need to counter that with what we may see as current or future definitions of abuse because these public attitudes have changed and we need to document that and to say what do we need to look at now or what will we need to look at in the future.

A good example was the Human Gene Therapy Subcommittee that spent six years educating itself about the nature of the questions to be asked in approving a protocol on gene therapy before we had a protocol so that they were looking at new forms of technology before they came on line, before they were there, so that we would know what ethical questions we needed to pose and technical questions, but primarily ethical, before they came about.

It requires pulsing and obtaining the public attitudes. This commission should try to do some of the same. Obviously you have to look at the current situation first. You are charged to do that by the President. But in that request to the agencies they are asked to talk about what they intend to do in the future and you need to push on that. We may need some fundamental changes and enhancements. You should be thinking as you go through your deliberations about what those might be.

PROF. CHARO: Well, now if you think about why it is that people do not get into trials, one reason is a kind of meta-involuntary protectionism, right. It is not just the vulnerable population, it is everybody. I mean, certain research is not approved because for nobody is it appropriate that they expose themselves to this risk. Okay.

So one thing very much follows your mention about the fundamental, very fundamental notions about the relationship between governmental authority to say certain risks are beyond the purview versus individual risk taking and risk seeking behavior. There are two other sections, though, in which it is not about protectionism and maybe they need to be dealt with separately.

Those are situations in which the exclusion takes place

because of the scientific value of the data that will emerge if they are enrolled. This is where, for example, you want subjects who do or do not have certain conditions because you want your data to reflect the interaction between what it is you are testing in either an otherwise healthy body or the interaction of the medicine with a particular illness. So the reason you are excluded is because you are not going to help the scientific enterprise if they enroll you.

The second is pure resources. That is that some trials are designed to be just large enough to generate statistically significant results and no more funding is available than that which will provide for X number of subjects and you are X plus one, frankly you are off the budget. You could be a perfectly appropriate subject but we do not need you.

Well, in those two settings where the exclusion is scientific or financial concerns, where people are trying to get in, by and large I suspect it is because they view this as a potential benefit to them, which raises the question of whether or not their concerns should be addressed in a research context or at the level of therapeutic access to nonapproved drugs, devices and innovative procedures, which has been tackled partly by FDA and is continually being retackled as the demands for access to innovative therapies --

DR. LEVINSON: And if we had national health insurance that last one would be --

PROF. CHARO: It would also be considerably different, I know. We have a major problem of tails and dogs here. But -- and with regard to those last two populations -- I am kind of thinking out loud. I am trying to figure out which is really the better setting for them to get access

to these innovative therapies. Because in the research context their monitoring and surveillance is much greater so that would bespeak a different attitude about whether the people who are not scientifically valuable or greater financing for certain research trials beyond what you need to see significant results.

Or is it better for them to get it through kind of regular therapeutic channels and FDA exception where you do not get the benefit of the monitoring and surveillance even though it is innovative. That really is closer to the model of therapeutic care and really it is FDA at that point of saying by and large, well, no, this is not available for therapy if it has not been fully proven.

I am just trying to figure out for that population because they are not about protectionism versus individualism. They are about separate issues. Where the best place would be to think about their lack of access, right. Is it trying to work at getting them into trials or trying to work at helping them get access to innovative therapy that is otherwise being held back, or something different, or just ignore them. Kind of a collateral damage.

Anybody have any idea?

DR. MANGEL: Jim?

DR. CHILDRESS: Yes.

DR. MANGEL: It occurs to me that there is one other population group that is vulnerable that we do not hear about too often and that is future generations whose interest may often be very antithetical to the individual interests of the research subjects and whose interests I think often have really not been spoken for.

DR. CHILDRESS: Sometimes they have been submerged under the heading of producing general medical knowledge that can benefit the future but we rarely go any more specifically than that.

Any response to Alta's question? I am not sure on some of these that actually we will get an answer today and perhaps ever. But some of these questions are very important for shaping the way we go about our enterprise keeping in mind some of these concerns as we deal with particular topics.

We also have the tentative point that Rachel has raised so effectively about pressing the agency's report for information about their enhancement measures. But also we have to reach a point and ask what we can do concretely and what we need to do. She has raised a question as to whether we should get at and others have suggested along these lines, too, about the attitudes.

What is happening in the complaints? What is their nature? How have they changed? What does this suggest about the kinds of concerns that subjects have? Of course part of the issue we are dealing with here are those who would like to be subjects and who are not so they are not making complaints because they are not part of that enterprise.

But any thoughts along those lines as to how we might move concretely on Rachel's suggestion? What would we like to find out in this area if anything? Part of this is a broad philosophical -- in a loose sense of the term, a philosophical enterprise, what kinds of concerns we have. But are there things that we could do concretely?

PROF. CHARO: What exists in terms of stuff that has been reported already about the subject experience and whether it is indirectly

through kind of compilations of complaints by type and number or in terms of surveys of people who have been subjects, or anthropological style narrative research, in depth interviews, et cetera? Do we know what is out there? Anybody? About subject experiences.

DR. CHILDRESS: Any comments?

MR. DOMMEL: It seems to focus on informed consent. There seems to be little complaint by subjects when there is adequate informed consent. If you turn to the Gulf War, that commission for example, that is experimentation, at least that is what is argued, and it is experimentation with inadequate or with no consent.

So my experience when I was with OPRR was that when fully informed one did not get complaints about outcomes.

PROF. CHARO: Would it be fair to rephrase issues about informed consent as issues of unfairly manipulated since informed consent has both kind of a technical understanding as it has been interpreted over and over by courts and agencies, and it also has kind of a common understanding in the way people throw it around now that they have seen the word used in the papers all the time? Or would that be too gross a generalization to say people are -- people get upset about feeling manipulated or lied to?

MR. DOMMEL: I think that would be fair to express it that way and that also then could include a body of individuals who were denied access, for example, and have their own complaints and it would fit with that same thing.

PROF. CHARO: Do we have anything that documents people who have never volunteered to be subjects to understand why people do

not? I mean, the quote that reflects actually a lot of my discussions with the colleague I mentioned who was on the African-American Medical, the quote by one African-American women in one of these pieces about how she really truly is likely to be so concerned about her ability to become a research subject now since very few of them were interested in seeing her as a patient struck me as being quite pertinent and a strong explanation for why many people might not ever even approach the investigator so that we are not going to be hearing subject experiences, but subject refusers.

Do we know anything more?

DR. CHILDRESS: Can anyone recall the advisory committee's discussion of their interviews with the 1,900 patients asking them not so much some of the kinds of questions we are concerned with, but one of the questions was whether they had been a subject or not, and why they had agreed to participate or had refused if they had been asked. And I do not have those data under control right now to give an answer. So we need to review that.

But anyway does anyone here recall? Yes, please.

DR. TITUS: (Not at microphone.) I believe what they focused on mostly was whether or not people perceived they were in a study or not and then they validated that against records to see whether people who thought they were in studies had actually been in studies. So it was a validation exercise more than anything else to see. And they found that some people thought they were in studies and they could never validate that they actually had been in studies. So I do not think they knew what to make of that. Were they really in studies? They could never conclude whether they were in studies.

You know, Dr. Charo's question about what do we know about subjects, my reading in the field is that we have asked subjects their experiences a lot but we asked them many months after they have been in the research and they do not have very good recall. We do not what they are being told. The research has focused heavily on their understanding of risks but we never know what they have been told. So we have this real gap in the whole process. We just know the subjects have some recall or very little recall, but we do not know much about that whole process. It has not been studied very well.

DR. CHILDRESS: They are really memory studies.

PROF. CHARO: Yes. But there are some studies I know that would be able to pick up on that. I mean, the degree to which there are studies that check what patients have taken away from these sessions with, you know, information delivered and what they retained say a week or two later. But not many, but we can get a hold of a few.

DR. CHILDRESS: This is one thing we clearly need to do then is pull together as much as we can in the area of subjects' responses.

MS. FLYNN: I want to go back just because I am still troubled by the comment that Alta made asking would it be a gross generalization to say that the problems of informed consent can be paraphrased as subjects believing that they have been manipulated or lied to. That certainly may be the case in some situations and I think it would be useful to get some handle on that.

But I also think at least for me with experience of subjects with mental disorders that the overwhelming sense that I get where people have concerns about it is not always a sense of there having been a specific

decision to withhold or to manipulate, or to receive, more a sense that the process is chaotic, that the process is not well structured, that the process is not well delivered, that there is not care taken to be certain that the information is, indeed, fully understood, and that there is still a drive towards consent as an event that ends in a signature rather than consent as a process that creates a partnership.

Now that to me is not the same as an assumption that would lead one to believe that there has been deliberate attempt to manipulate or deceive. The results in some sense will certainly be the same but I think it is important to get at the differences there.

PROF. CHARO: Laurie, last night when we were talking after dinner about what we were interpreting the phrase "community" to mean as it was being tossed around at the last meeting, we found ourselves talking about ways in which groups of people who might be the subject of a recruitment effort interact or might be the people who are closely related in the case of those with mental illness, to those who had been recruited might interact differently. I wonder if you can remind me more fully of what it is you were saying about the experience you had with working with a more close kind of partnership relationship?

MS. FLYNN: I am not sure if I am recollecting. Are you referring to the particular interaction that I described with -- I will take a moment if this is useful because it may give some indication of some practical ways in which we could move positively around some of these issues.

Several years ago at the time that there was considerable really publicity around the case at UCLA with the schizophrenia research, it

was a heightened, obviously a heightened awareness in the research community that I interact with, around risks to these subjects and appropriate consent and so on.

And I was asked along with a legal person on my staff to interact with an IRB locally. It was the first time my national organization, well known for its interest in these areas, had been asked to do that to my knowledge. It was -- the IRB administrator at the behest of the investigator who asked us to come out. And it was quite an interesting event.

The investigator had been before the IRB with a protocol involving a medication study which was largely an outpatient study which was dealing with individuals who had a significant mental illness impairment. The first go round had not been approved and there were considerable concerns on the part of the IRB about appropriate informed consent procedures, as well as the appropriateness of an ability to provide adequate monitoring of the subjects in the outpatient trial which involved a drug washout period. So we had a whole set of very difficult to manage circumstances.

We were given a copy of the research protocol to review and asked to come in as lay individuals well familiar with the subjects, supportive of the need for the research enterprise, and practically familiar with what it is like to deal on a day to day basis with an individual who has a disorder that can be difficult to manage, particularly when undergoing a change in medication.

We had some very concrete and practical suggestions. We found our suggestions were very well received by the IRB. There was quite an extensive discussion. The investigator found them very helpful and

subsequently notified us that after amending the protocol the protocol was approved. So it was from my standpoint a very positive, inexpensive, practical and ultimately quite useful way for the lay community interested in research, very concerned about protecting human subjects, to be partners with an IRB on this particular case.

So that to me is the kind of community participation, if you will, to use the phrase to mean community of those interested in the disorder, interested in the subject population. It seems to me quite do-able and was very much appreciated and really led to follow up discussions about availability for other kinds of such consultations down the line.

This was the first major study that the IRB had been asked to consider of this type and we were told by several people later that it probably would not have been done had we not been able to offer some practical ways in which it might be managed, that they were just likely to just say as you indicated earlier, we just cannot take this risk.

It was an interesting experience.

DR. CHILDRESS: The background to this particular discussion about community was a comment at the first NBAC meeting when people were expressing some of their concerns as well as some of their hopes that Zeke Emanuel made regarding the importance of moving beyond the Belmont principles to incorporate some of that community.

Now community can be thought of in so many different ways and this is one concrete example of we can have community involvement in a very significant way in shaping a protocol.

One larger question in terms of shifting paradigms and principles is whether we need -- whether something like this could be

brought under the heading of the kind of requirement say of fair and just participation. So all you need to do is reinterpret some of the principles that are already working.

When I go back to these principles let me emphasize that IRB's often have to appeal to these when they are trying to think through what might be covered by the regulations in place. So these serve as kind of general points of reference. Now obviously one interpretation of justice would require -- could require this community participation.

Is there some concern being raised by the community that we go beyond that? It seemed to me that in part, as Zeke was concerned, that we attend to more perhaps to the benefits of the community and getting that maybe not only to the future generations, but also the more immediate community broadly conceived and that perhaps we neglected that. Well, maybe in some ways that would be captured in some of our earlier concern about access, but it clearly goes beyond that to talk about the benefits of research for the community as a whole.

So there are several different kinds of concerns that can be brought in and I think one of the questions we have to raise and keep in mind as we are dealing with our particular topics today is what we want to formulate, if anything, on a general level that would be comparable to or simply enhancement of the kinds of Belmont concerns. What would need to be redone in that regard?

Now this is a kind of thought process enterprise that we would obviously have to undertake over time and with help from staff and perhaps with independent contractors as well if we decided to go in that direction. But part of what is coming out of this discussion of the changing

context, which is changing the nature of research, changing the nature of funding, changing attitudes of subjects and potential subjects, and so forth, would be to think through again the kinds of general moral considerations or ethical principles, which again is one of the tasks that our charter asked us to focus on. Sort of the level of ethical principles, not on the level so much of evaluating particular protocols, but on this kind of level.

DR. CASSELL: Well, with respect to persons -- because when we talk about persons, the sense of respect for -- in a political sense of respect for persons, we hold these truths to be self-evident of all persons.

PROF. CHARO: It says all men actually. It says all men.

DR. CASSELL: It actually does not say all men. Does it say all men?

PROF. CHARO: Uh-huh.

DR. CASSELL: But it means person.

(Laughter.)

DR. CASSELL: Lately --

PROF. CHARO: No, it says all men are created equal and women are created better.

DR. CASSELL: Wait. You are coming to the point I am about to make. You just made my point for me.

PROF. CHARO: I am sorry.

DR. CASSELL: The word "person" expanded out greatly and changed -- what you did is just pointed out one of the changes. Women have become persons in public only in the last two generations. Persons with disabilities have become persons in many senses only in the last five

years and so forth.

The inclusion of the word "respect for person" is a very -- treat the patient as a person, which actually means treat the patient as if the patient were a person. It is a thing that patients now are persons whereas a generation ago patients were not persons in the sense -- in the common sense that you went to the bedside, put the person in bed, and walked out with a family member into the corridor to have the conversation. The patient was a patient, the person was the family member.

So the concept of person in the 20 years since the Belmont Report has changed markedly on the one hand and then there is the nature of the particularity of person. If we are to be respectful of persons -- have respect of persons then it enlarges the sense of that to have respect for the particularity of persons. In which case the word "community," which for linguists is often a language community, your community is a language community in the sense that it does not -- it has the sense of shared of meanings for words that are different for the rest of us.

So that a research that addresses a particular subject and uses words for it is using it in one set of context where there is a community, a special community, the community of persons with mental illness, will use the same words very differently. So when we extend the sense of person or respect for persons, or we understand it, in a sense what we do is make it clear what the word "person" means now as opposed to what it meant originally, or as opposed to what it meant in the Declaration of Independence.

So -- that is not a small matter from my own personal hobby

horse. It is a central word coming to know what, in fact, it means to say someone is a person or if you respect someone as a person. And I think we have a role to play in that but our role is once again --

DR. CHILDRESS: Okay. Let me pull some things together and see what your response is. The original Belmont Report actually emerged at the end of the reflections of the national commission. It was, as I recall, the last document put out, right.

We started with the reflections on the general changes that might well occasion a new reflection on the kinds of principles at work, whether we need to expand them, whether we have something like persons in the community, sense of justice and so forth, as well as focus on the negative side. What is the sense of injustice in terms of complaints and violations? Has that changed over time?

So the broad philosophical enterprise is something that will go on as we engage in our particular topics. It may not be something that we can resolve or even should resolve at the outset as long as we are simply attentive to the kinds of shifts that are occurring in our own thinking or thinking of others as we approach the particular problems. But it may well be that we will want to at least offer an addendum to Belmont when we look at it and taking account of the kinds of changes that have occurred.

So I am not suggesting that we make it a top priority to redo Belmont but that may be something that might emerge as we go on.

DR. CASSELL: Well, but I mean in terms of addressing those principles to show how their meanings have changed. That is not redoing as much as making clear -- it clarifies those principles even in that respect.

DR. CHILDRESS: Right. By offering a richer, deeper interpretation.

DR. CASSELL: Right, there you go.

PROF. CHARO: Jim, I do not know what your plan is given that we are running ahead, but you may want to be saving time, but I would find it actually valuable somewhere along the way, separate from the specific topics, to try and keep going for kind of a list of what people might have meant or would now like to mean by community because you can imagine many different variations on it.

But with regard specifically to the concept of respect for persons in the Belmont Report one other thing that -- I do not know if you are going to call it community or whatever, but dovetailed to it is something that comes up in the context of the Loretta Compliment piece where she goes through the justifications for research.

DR. _____: Could you speak up?

PROF. CHARO: Oh, I am sorry. The Loretta Compliment piece where she goes through the justifications for research in the context of children and where she makes an argument of a certain point that parents ought to be entitled to expose their children to some amount of risk that is similar to that risk that they expose their children to all the time for the purposes of moral and other training. And that parents are allowed to balance benefits to the child or benefit these kinds of things against other family members, which is where she differs from a kind of atavistic individualistic analysis of what is in the interest of that child outside the context of the family, right. She has now -- has the context of the family and therefore she comes to different conclusions about what is acceptable.

It seems to me that discussions about community then raise the issues that she has tackled when she tries to dispute both the authors that, you know, were arguing in terms of kind of an altruistic approach, we are all part of a larger community, and programs, and kind of individualistic approach because it was not clear to me why you could balance benefits to the family in the decision to allow children to be enrolled, but you could not benefit -- you could not balance advantages to a larger group of people beyond the family. It seemed to me she is moving from the atavistic individual to the atavistic nuclear family unit as her unit of analysis.

So this notion of community and altruism I think --

DR. CASSELL: The community does not pay the same price if the child suffers as the family does.

PROF. CHARO: Well, it depends. In some places they do and in some settings they do. It depends on the social safety net. It depends on what you are defining as the family.

DR. CASSELL: Well, it could. In your community it could. If one member is injured, right, they could suffer.

DR. LEVINSON: Or any genetically --

(Simultaneous discussion.)

DR. LEVINSON: This is a point of intersection with the Genetics Subcommittee that met on Friday talking about what is the patient, what is the community, what is the family, and how information given to one member has a ripple effect. And your definition of community has to be altered when you are talking about the national community to a larger sense or the global community, or the particular components

sharing the genetic information that would be more immediately affected.

PROF. CHARO: So that I am beginning to feel like there are two very distinct senses of the word "community" that come up and I am not sure which ones will turn out to be easier to incorporate, if any. One is the sense of community consultation, notification, involvement of protocol design, involvement in receipt of research results, debates surrounding access to interim results. That is one whole collection of what they might call community.

Another whole collection really focuses on the respect of persons issue and how it is that we define what is a benefit to a person, what is considered -- because benefit to the extent that it is defined to include not just physical benefits, but also the benefit of being a participant in an exercise of social good, right, has arisen in other context. It has to do with minors with sibling to sibling kidney transplants which have been by and large justified by the notion that the sib who would live regardless would feel terrible if the other sib died for lack of a transplant. So on that basis the psychological benefits have been used to justify sibling transplants.

Having seen it arise there in both a kind of fast talking morally context along with a kind of emotionally real context, you know, I feel that it is legitimate to struggle here for exactly those same things. Because that would go right to the basis of how it is that some of these categories that we have been using the regs now are constructed and the appropriate levels of permissible experimentation and significant review and monitoring are implemented. That all has to do with that basic risk benefit balancing.

So I guess I am asking whether or not we can think about persons more broadly without getting into such a mess that it becomes impossible to regulate?

DR. CHILDRESS: And I think there is that third sense, though, of community welfare, common good, that goes beyond either of these, particularly in terms of the benefits of research. So I think we would have not only the two you mentioned but at least that third and probably some others as well. Just as, during a much more individualistic period, those working on Belmont had to try to sort out ethical thinking in terms of categories that were widely used, it seems to me that we may well want to attend to these.

Now one reasonable thinking, though, that along the lines of the national commission we may well want to do it concretely, is that you moved very effectively from the concrete examples, for instance on children, and in the process of that kind of reflection we are able to tease out perhaps some of these concerns and the way in which we might reflect them very differently than earlier.

So I agree that this is an important enterprise and one that I think we ought to keep in mind as we are moving along. I am not sure, though, that we want to try to resolve it now rather than simply flagging the kinds of things that need attention as we move along. At least that is my sense, but obviously it depends on what --

DR. CASSELL: Well, we could try to resolve it in the next four minutes.

DR. CHILDRESS: Well, if you agree with that sort of general approach that it is something to keep in mind and we need to work on as

we move along. We do have, though, the question I want to ask about each topic we deal with, and let me just ask it and maybe we can take our break in four minutes.

We had a question about attitudes of subjects. That I suggest we do need to get as much literature as we can and see where things really stand and see whether we need, indeed, to try to commission some other study.

But any further comments about that? I mean, that is just flagging something that I think we need to look into further and then see whether we need to do something on our own or commission someone to do that?

PROF. CHARO: With the caveat that if it were possible to get something about people who do not want to be subjects, to understand better the refusal or the disinclination, I will put it that way.

DR. CHILDRESS: And for those around the room, if you know things, I will not ask you right now to do it orally, but if you will check with me right after -- over the break and share information with me so that we can make the literature available to members of the commission.

DR. CASSELL: Did we pick up multi-institutional research in the changing paradigm?

DR. CHILDRESS: No, we did not. That is one important -- and if you are looking, for instance, at the report from the Pennsylvania Center for Biomedical Ethics where some materials that Charlie McArthur and others have prepared is incorporated in terms of the changing nature of the research. I had that in mind when talking about the changing nature, but I did not focus on it. Do you want to say something about that?

DR. CASSELL: Well, in some ways the comments about multi-institutional research are the exact opposite of what we were just talking about before because multi-institutional is often multi-national research as well. A lot of the cardiac research now has been done in a number of different countries and there the assumption -- the basic assumption is that all subjects are fundamentally the same. And the differences between communities are erased by the virtue of a commonality of coronary arteries.

Yet we still have the sense that there are certain threats in that kind of research that are different, that is the mass threat. You would not want to be the one that holds up the research that is now going on at 23 different institutions and you are the only institution that found the consent form inadequate so that has a -- and I can remember in my IRB time what happened when we had some doubts about one of those consent forms. There was just a feeling you could not do anything about because after all, look at it, it was all over the country, the same kind of thing.

And so there is some concern about how those problems should be adjudicated rather than being dealt with like that by multiple institutional IRB's where there might not be a special way to deal with multi-institutional research that protects the subjects. And also to keep the fact that they are not all the same from being effaced from understanding.

DR. CHILDRESS: I think that is another important shift that we have to attend to as well.

PROF. CHARO: Can I just pick up on the agenda as briefly as he did then?

DR. CHILDRESS: Sure.

PROF. CHARO: Somewhere along the way a serious consideration of private versus public sources of funding. It has been my casual observation that an awful lot of the privately funded research takes the form of "me too" research for basically marketing purposes rather than generation of new knowledge. I would generally be interested in hearing whether or not that should be a significant factor in figuring out how to approach the reviews of research.

DR. CHILDRESS: Okay. I propose that before we take a break we think for a moment about what follows. Among the list of topics there are three that individuals on the committee have been asked to focus on. Informed consent is one and if it is agreeable with the group I propose we pick that up immediately after the break.

Then vulnerable populations. Obviously we have to talk about the range of those to be considered. The two examples focused on problems that emerged and also interest of subcommittee members were children and cognitively impaired subjects. So I propose that we hit those three areas and if that would make sense to the subcommittee. Does it make sense?

PROF. CHARO: Sure.

DR. CHILDRESS: Okay.

PROF. CHARO: Yes.

DR. CHILDRESS: So we will do those and we have to also think about IRB's as an institutional mechanism for dealing with these topics. Then we have a lot of other things on the list as well, including compensation both for participation and for research related injuries, and the like.

The question we have to ask at each point because we have to come back at the end of the day, not only dealing with the things that we would like to cover from these topics, but also to decide what is it we can do and what should we do immediately. What should our immediate agenda be and what should it be over the next year?

Thanks. Let's take a break.

(Whereupon, a break was taken from 10:00 a.m. until 10:24 a.m.)

DR. CHILDRESS: While we are gathering we have had some new members to the audience and newcomers. Are there any others who have arrived who have not been introduced yet?

DR. RIKEN: Sandy Riken from OPRR.

DR. CHILDRESS: Okay. Anyone else?

VARIOUS TOPICS FOR DISCUSSION THE REMAINDER OF THE DAY

DR. CHILDRESS: Okay. All right. Thank you.

We will start with our discussion of informed consent and ask Eric Cassell to lead off that discussion. This is one of the topics that several members of the commission as a whole have suggested that we look into.

So, Eric, if you will kick off our discussion.

DR. CASSELL: All right. A person and his chocolate chip cookie are not soon parted.

First of all, I want to say very clearly that nothing I say on this subject should be taken as suggesting a reduction in measures now in place to protect subjects of research. Nothing. Forward motion is not done by going backwards. It is not a question of changing or taking away

protection, it is a question of understanding it better and enlarging it so that it works better.

As we all know, and as the document that we have in front of us makes clear, the consent to research is probably the basic or the fundamental rule that followed on the Nuremberg trials that all participants in research consent and then it has been revised through the years. Fifty years ago, the Helsinki revisions started about 30 years ago, the National Commission revisions are about 20 years ago. And I think that for us to understand this we should see what we would have to do to move forward past merely refining or solving the fine points of consent.

I do not think we would serve our purpose as a commission if we just tuned the regulations. It is not that those things are unimportant because, in fact, tuning regulations is a very important function. But it is not a final function.

We have been talking -- I am happy to see that we have been talking for a good part of the morning on what has changed during this period of time. So I wanted to make some anecdotes to make it clear.

First of all, I have been practicing since 1961 and in the 1960's when people had cancer clinicians did not tell them what their diagnosis was. It turned out in some of the research that had been done in Britain in an era that was equivalent to our's perhaps 15 years later that patients had a pretty good idea of what was the matter with them, but it was not a subject of conversation between the patient and the physician.

One reason it was not is not because somewhere in the late '60s, early '70s doctors suddenly discovered the truth as though they had not known the truth before or that they were previously liars and now were

morally refined, it is the relationship of persons to their disease that had changed dramatically in just those few years. Not actually, but in conception.

In the early '60s the relationship of people to cancer was that -- was passive. If you had cancer it was a -- if you survived that was wonderful, but it was a sentence of death and it was not considered that there was anything you could do. And in the absence of anything to do, telling people about it seemed to serve at the time no purpose.

It is not that there were no debates about that subject. There were a lot of debates about it. And then as you all know, nowadays we not only tell, it just drops out of our mouth like little truth clots. We do not hold anything back anymore. The problem that my patients say -- well, they are going to tell me the problem is not telling -- holding anything back, it is telling without any purpose, just talking.

But something else changed in the same period. In 1954 I was a fourth year medical student and we were doing a piece of research that my department was trying to see whether streptokinase, streptodonase (?), would be a useful treatment for heart attack. I want to point out that was 1954. The concept at the time was that heart attacks are caused by clots in the coronary arteries. You find that familiar. But, in fact, that concept went in and then went out, and then came back in again.

But in 1954 that was the concept and so we needed a subject to do this on and the subject had to be a Bowery bum with no family. That is not because Bowery bums with no family had coronary artery disease, it is because they were not -- he was not going to be told what was to be done. So the thing was started and about 24 hours into the

research the constant electrocardiograms that we were doing began to show irregularities and then the research was stopped for fear that he was being done damage.

So I want to point out several things. First, he was not informed and, secondly, the research was stopped for fear of hurting him. So that the idea that somebody taking care of him was informed, it is that he should necessarily know. Now nobody would do that now. Nobody. Maybe in some back room research somebody might try that because they were trying to find some, you know, something, but in general that is gone. It is gone. It is gone. It is gone and good riddance.

But the important thing here is that in this period of time from 1954 until perhaps the late '60s that had not changed dramatically and now it is just an absent thing. So between those two things, the difference in the relationship of persons with a disease, doctors to patient, and in our attitude to research, we have to see that there has been this tremendous change.

Not only that, but I was on an IRB at Cornell before the law required them. We had an IRB and our biggest problem was the oncologists. It took about two years for them to get it. The idea was not to write a consent form that could fool a patient into consenting, but to be honest without making a consent form that you could die from because there are consent forms that you can die from.

We had -- actually just parenthetically, we had a consent form that started out "I realize that I am at increased risk for sudden death..." and went on from there. We thought that probably could be put in some other fashion. In any case -- and, yes, get across the point.

But in the early days the issue was here was a committee you had to get around. But within five years that aspect of getting around the committee had changed and people pretty much knew that they were -- that they had to meet the committee's requirements. But that is not to say that at the same time there was not research going on that met no standard of protection if it were not for the committee and that is the point, that the committee serves a very important need.

One that comes to mind is the Burn Unit wanted to do a study using a placebo against enipromine (?) as a pain reliever. Well, enipromine is no pain reliever in anybody who has got a bad burn. If anything, compare morphine. When we suggested that that seemed unethical to us, that at least it should be against morphine, they said, "Well, we really do not know whether morphine relieves pain." Well, the rest of the medical community knew it.

So that even though that committee had rules and it stopped that kind of research, in fact protocols were being submitted that not uncommonly investigators had to be reminded that they were not doing this just to satisfy the committee. They were doing this because of a basic need to protect their subjects.

Now with that as a background we should see whether, in fact, in the subsequent refinements of the regulations and questions of consent bracketing the important problem of subject's lacking capacity, this whole conversation brackets that.

DR. CHILDRESS: And we will get to those.

DR. CASSELL: And we will get to those as separate. The reason it brackets it is that that is such a knotty problem. It was not solved

then and it is not solved now, and we will get to it. But bracketing that, we have to see whether we could not create for ourselves a more forward looking understanding of consent and the needs for consent.

So I would like to look at some of the elements of informed consent very quickly. First, the idea of informed. What does it mean to be informed? Well, there is a persistent difficulty with the information that is put in consent forms because as Hans Ingelfinger -- Franz Ingelfinger (?) said many years ago, "There is a distinction between informed and being educated."

It is common knowledge that people can read a consent form. Even with a requirement that it should be in plain English that the people should be able to understand it without being physicians -- as you all know who have seen consent forms that requirement is breached more than the performance mostly because people do not know how to write plain English. They do not know how to write plain English in their every day life and they certainly do not know how to write plain English when it comes to consent forms.

So that the information is there but the degree to which it has meaning for the subject is not clear. In studies that were done 20 years ago of consent forms repeatedly it was shown that the subject did not remember the content of the form that they had signed the day earlier, the week earlier, and so forth. That has been shown again and again.

Now I had a recent experience actually just about ten days ago of a family member being given a consent form to sign by the surgeon. He is a surgeon who is a friend of mine and he is a wonderful surgeon, and the surgery was important, and that consent process met no requirements

other than the name of the surgery and would you please sign consent for this.

Now why in heaven's name would anybody sign a consent form when they really had not been informed beyond what the operation itself was done? Because they trust the surgeon. And we come to understand that the idea of informed -- the idea of informed is a difficult one because of not only the issue of meaning and -- because of what somebody does in the process.

But before I go on I would like to say there is another problem of information and that is time. I signed a consent form in May 1962 or '92 or '102 for research and then three years later I am still a subject of the same research and I am still covered by the same consent, and yet I have no more memory of what that consent form was or what is part of this research. I am somewhat hoping that the investigator does.

Because if it is like any other research it has changed subtlety in the intervening period and data has come in and altered what is really going on with no real reason but just that that is the way research goes. If the thing is not working right the way you originally designed it, it ought to be changed somewhat so it does. Yet rarely are subjects given an opportunity to review their consent because the research has changed.

So on two elements of time that investigator -- that subjects forget what they had, time passes. And also that the research changes. The issue of time enters into the business of being informed.

I do not know -- I should put it differently. Most of those problems that I just mentioned and the ones we could go further into cannot be solved by changes in the regulation or by the way the paper is

written. That is comprehensibility because, in fact, there have been attempts to do that, to show people how to write a comprehensible consent. But I do not know if we got 100 random consent forms now whether they would meet the standard of comprehensibility that has been published.

So just on the issue of inform it is problematic at its best. The next is the problem of consent.

The subject of any consent, whether it is for clinical -- whether it is for research or treatment, knows something that no one else can know. No one else can know. And that is whether that what is proposed meets his or her needs, concerns, fears. Or put another way, what it means to the subject. That is the absolute particularity of the research subject, the patient. It cannot be any other way. Meanings are idiosyncratic. It makes the question of consent itself seem like all judgments.

A consent is a judgment. I make the judgment to go along with this or not. Judgments, as we know, are considered to be particularly idiosyncratic in the sense that you cannot -- there are no rules that apply in general to the particular. This is a perfectly good example of applying the general to the particular. The general being what is proposed and the particular being the person who is about to consent.

Now that is actually not true that there are no -- that it is entirely particular and idiosyncratic or personal because judgments made perfectly clear are also social. There is an audience for every judgment. When you get that consent form there is an audience to that consent form. There is the audience of people you wonder would approve if you signed or

did not sign. In your community what would the other people think if you backed out when everybody else had said yes and now you back out? That is an audience for that judgment and it is an audience that is very powerful.

So that there are that audience. Then there is the audience of am I a good citizen, am I a good whatever it may be. Is it right to do these things? Those are personal private decisions in the sense that they have only to do with that person. They are personal and private in the sense that a person belongs to a social group and so that social group is always present in the consent. We know that.

We know that there are certain situations where coercion is a real problem. Prisoners, for example, and other situations like that. But coercion is always present. Remember you can be coercioned into not signing just as being coercioned into signing. It is not simply a question of whether you do something. It is a question of you do or you do not do something.

The idea that a judgment is absolutely free and independent, that there is nothing else that bears on it than your own desires and concerns is just a myth. There are very few judgments we make that are like that. All judgments are political. They are political in the sense of Aristotle sense of the political in relation of the person to the investigator, to the person, to the other persons in the study. So it is not just what other people think. It is how do I stand? Because will I lose? Will I be passive? Will I lose my independence and so forth? Which are very important and very powerful.

The judgment of consent is social in another sense. No matter what the form says, whatever the form says, it spells out in such

detail that not one iota of the research proceedings is not on that consent form. Something like Barney Clark's consent form. I do not know if any of you know it, but it was 17 pages -- 14 pages long.

Just as an interesting side, Barney Clark's consent was 14 pages long. The requirement for a subject in that research was that they had to be within two days of death from congestive heart failure. That was Barney Clark and here is the 14 page consent form to make sure they understood what they were signing it had to presented again on the following day. Now in a funny way that should be -- we should all keep that wonderful image in mind.

Barney Clark signed that. Why did he sign it? Why would anybody sign a consent? Who would sign any consent if you did not trust the investigator? Supposing you understood that so and so investigator was totally, completely and absolutely untrustworthy, you knew it for a fact, would you sign anything related to that? It would not matter what that consent form said. Because the issue of consent is, in fact, consensual.

It requires a relationship between the person doing the research and the person consenting even if the person consenting does not have any idea who is doing the research except in the individual -- in the multi-institutional thing who has no idea who is up there making the determination of when to stop a project or to start. It requires trust then not of an individual but trust in the social organization that does it.

A consent form is a social document like a contract. We in bioethics have concentrated on the subject's side and on the formal side. Almost exclusively on the form of the consent and on the subject. Now in part there is a very good reason for that, but we have not concentrated

nearly enough on the fact that it is a social contract. In a social contract there are two parties to it and that our interest in the other party to the consent, that is the investigator, has not been nearly enough.

I think this commission can begin to examine the question of the social environment of consent, the knowledge, commitment and trustworthiness of the investigator. The word "education" we already said a number of times.

I think -- I do not know about the rest of you, but I have the experience yearly at Cornell of participating in the education of young investigators who are required by regulation to have -- I do not know how many hours of -- in any case I do my part in the seminar and there sit eight or ten young investigators trying desperately to sleep with their eyes open learning the ethics which is necessary to do their work. To put it another way, learning how to get around that thing between them and their Nobel Prize.

I am characturing it, but I am characturing it much too closely to the truth. They do not understand the subject as a necessary participant, cooperative participant in their search for that Nobel Prize. They have no sense of that. But they are not there to get around the regulations or even comply with the regulations. They and that subject are a lot together. There is no way for them to find out what they want to find out without the participation of that subject.

We could make that even clearer by getting a set of subjects and showing them how to cheat. Just taking one research project and showing all the subjects how to cheat so that they destroy the research, which is really very easy to do. In some of them all you have to do is trade

urines around. Nobody would think of doing such a thing because wouldn't that be awful on that side, but we do the equivalent thing on the opposite side through lack of education.

So my own sense of it is that recognizing the bracketed question, the subjects without capacity, which we have not started yet and which is going to bend our heads, i believe that we have to examine these other relational social aspects of the question of informed consent in order to move forward.

Thank you.

DR. CHILDRESS: Thanks, Eric. If I might just summarize your bottom line. Basically you have argued that the way we have understood informed consent has really limited us too much to the subject side at a particular moment in time as expressed in a consent form and that what we really need to do is to take a broader view of the temporal dimension and also the social context. The best way to do this from your standpoint is through education rather than through changes in regulations. That would be the bottom line?

DR. CASSELL: Yes. My bottom line is not a couple of hours of education, but we would not consider for a moment that an investigator could do biochemical research without knowing biochemistry. I think the investigator cannot do biochemical research with human subjects without knowing clearly an understanding because he or she has been well taught the ethics of research.

DR. CHILDRESS: One question would be -- and I am sure the other kinds of issues comes up for subcommittee members as well -- would be what we need to know in addition about the informed consent

process. There is an RFA that has gone out and I guess perhaps it will be awarded some time in the next months. Is that right? For empirical research in informed consent.

Anyone like to comment on that as to the nature of what we might expect from those studies? It is probably too early to know given the fact that, I guess, everything is still in the process. But I am assuming we probably could not get the results from whatever studies are funded there for several years.

DR. CASSELL: Is that the first research in recent years? Is that right? Does anybody know?

PROF. CHARO: I think I know of at least one study out of my institution that takes a limited view of comprehension and I can track down if it ever got completed and published. I know that we reviewed the research for susceptibility so I know that it had been planned.

DR. WICHMAN: I am not an expert in this. I am Allison Wichman from the Clinical Center. There is a lot of research on informed consent. The unique aspect of this -- the grant that you are referring to is two NIH grants. One a public announcement. I cannot remember which is the RFA and which is the public announcement. But the National Institute of Mental Health has asked for proposals looking at informed consent for impaired subjects or those with mental disorders.

There is another one that several institutes and government groups, including, I think, the Department of Energy, but I am not sure about that, but a number of the NIH institutes, including the Human Genome Project and NIAID, and others looking at asking for proposals on empiric research in just about any aspect of informed consent.

The unique feature of this is the NIH funding which is a major step forward in the attention to empiric research in informed consent.

DR. CASSELL: We could do with a bibliography, couldn't we?

DR. CHILDRESS: On that, yes, we could. That is another area where we need to get up to date on exactly what has been done.

Yes?

DR. WICHMAN: But there is a huge literature on empiric research in informed consent.

DR. STOKLOSA: I just wanted to add -- I am Janice Stoklosa from NASA. At the Human Subjects Research Subcommittee meeting that the agency had last week NSF provided a discussion of the current research in this area. It is my understanding there are two recent citations, 1994 and I think one later, that have reviewed the literature in this area. NSF is going to provide us with those citations and I am sure they will provide you with those citations.

DR. CHILDRESS: Would you also copy them to us when you get them?

DR. STOKLOSA: Sure. I would be glad to.

DR. CHILDRESS: Thank you. Okay.

Yes?

DR. PETERS: There is also research, GM funded research, on the informed consent for BRCA-1 testing for breast cancer by Jill Gilbert (?) at Johns Hopkins.

DR. CHILDRESS: Okay. So we will pull together the

literature available and see exactly where current studies are going and we will be as up-to-date as possible on that empirical side.

What else do we need to do in response to Eric's comments or beyond Eric's comments?

DR. BRITO: Well, I was just going to say that earlier Laurie mentioned the word "partnership" in terms of informed consent and doing research. I think it is -- the bottom line, which Eric was saying, and correct me if I am wrong, is basically developing programs in which investigators are educated appropriately to develop this partnership so that there is no misunderstanding of when people sign consent forms. No misunderstanding of what that research may involve.

One of the problems I have had with informed consent and IRB's, et cetera, is that it seems to me that when people sign consent forms there does not seem to be much of a responsibility or -- how do I say this? The investigator is not held accountable for having educated that participant appropriately. I think maybe that is one of the ways we need to start changing the way we look at informed consent.

In other words, there is no proof that if someone signs informed consent that they truly understood that and there is no co-signature by the investigator saying that they feel that in the person's capacity they did understand the informed consent. So I think one of the ways -- practical ways you can look at this is maybe devising ways of clarifying the educational process that goes on between the investigator and the participant in informed consent in a research study.

PROF. CHARO: I think following directly on to Arturo's comment, because it is so widely recognized that frequently no matter how

written, as you have pointed out, the process -- the phenomenon of obtaining a consent form signed is forcible. I find myself interested in your conclusion, Eric, that the appropriate effort here might be of education as opposed to regulatory reform specifically.

I think that the focus on the use of documentation of consent in the form of these consent forms has created a lot of ill-will between IRB's and investigators that undermines the function of IRB's because to the extent that everything focuses on the form, IRB's focus on the form -- Gary, you said that a lot of the complaints had to do with forms.

That means that you worry about word changes and from the point of view of the PI who is waiting to do the research all this fuss about a word here or there feels like it is nonsense and it feels like rearranging deck chairs on the Titanic because everybody recognizes it is forcible. The underlying process is of obtaining a signature on a form as if that actually documents that somebody generally understood something.

I know from some of the protocols we have reviewed in a multinational context where notions of autonomy and consent are fundamentally different than in the U.S. that we have reached out for different kinds of solutions other than the use of a form to document an otherwise unmonitored, unreviewed conversation.

So that the focus became on the process of information delivery over time rather than on the form and that one would think that was used to make -- one of the conditions of approval to a particular protocol had to do with the use of a consent monitor who simultaneously served as both a monitor of the discussions and as a facilitator from the point of view of the subject of continuing questioning so that it -- without

particularly proposing that necessarily as a solution in the United States, it struck me that that is not an issue only in another country. It could be the beginning of a way to think about what we are trying to accomplish and how it is best accomplished.

To conclude I would also say that kind of thing also begins to tackle a secondary problem which you identified, and those are the structural incentives driving various parties to these arrangements that work against using a simple form. The structural incentive on the part of many PI's is simply to recruit as many people as possible. Structural incentive on the part of a physician in a therapeutic relationship with a patient who is thinking about enrolling that person in an experimental trial where I think there is more reason to believe that more frequently there is an actual benign attempt or beneficent intent rather than a mere recruitment attempt.

I think they are two varied situations in terms of the kind of implicit trust, the degree to which the subject will, in fact, just hand over decision making authority based on that trust, et cetera. And that by focusing on the process and structure of the relationship and trying to find perhaps some other mechanism to be embodied in the regs other than just the form we actually might be able to make some more progress than simply education of the current kind of documentary obsession.

I do not know if it is realistic at the implementation level so I throw it out as a thought.

DR. CASSELL: Well, you know, there are two -- I think there are two fundamental ways of going about moral regulations. One is to regulate it legally through regulations and the other is to educate. I do not

think they are mutually exclusive. But moral regulation is our regulation and the special forces and educational forces that achieve that I tend to believe in the long run are more effective.

On the other hand one of the social forces is regulation -- is legal regulation. That is a central point. That is what changed. The investigator climate -- investigator climate if you want -- climate in the United States was all these regulations. It changed the way people viewed it. There is nothing wrong about that.

My other question is now doing the next step.

MS. FLYNN: Given that we have been taking about a change up in paradigms --

DR. CHILDRESS: Speak up, please.

MS. FLYNN: Given that we have been -- just following up on your comment talking about potentially a change in the paradigm where we are seeing research subjects and the research community as having a less adversarial and more moving towards a partnership kind of role, how does the notion of a consent monitor square with that? Does not the notion of a consent monitor, depending upon again how it is positioned and the individual's relationship to the institution, and so on, does that not sort of reintroduce that sense of adversarial lack of trust, lack of common ground into the relationship?

PROF. CHARO: When I work in foreign countries I frequently work in a foreign language that I only know how to use imperfectly and I often have the assistance of somebody who is simultaneously a translator for those moments that my language abilities fail me, and also turns out to be a bit of a cultural translator.

Often he will translate for me the broader meaning of a comment that came back to me that literally seems evident but again in a context that I am not familiar with. I do not know how to appreciate the remark.

And I think that there is a role for consent monitors of that type in which we recognize that the -- even if you are trying to create a larger role and respect for the subjects that there is always going to be a phenomenal unevenness in the power dynamic and in the technical knowledge. And to the extent that there is an unevenness to the disadvantaged investigator, kind of a personal dynamic, that is never going to be given the regard that it ought to.

So the role of the consent monitor we saw as being, number one, a constant kind of double checking of what was really comprehended with kind of a notion of the fiduciary duty, the loyalty being to the subject and not to the investigator. Separate from the investigator, the loyalty to the subject.

What did you really understand and can I help you figure out what the implications of those are so that you know what you might want to ask next? There is a person working with you throughout the process so that you appreciate it each time -- at each moment how things are changing and whether you might want to back out, et cetera, et cetera. I do not think it is inconsistent with more of a partnership model.

It may, in fact, facilitate greater sensitivity to things like the psychosocial and kind of economic risks that are most difficult for PI's to anticipate and document and even for IRBs to anticipate documents which are an important part of the informational exchange now.

MS. FLYNN: The way that you are describing it makes me believe that the word "monitor" is perhaps not the word we would want to use.

PROF. CHARO: Okay.

DR. CASSELL: How about facilitator?

MS. FLYNN: Because facilitator, I think, or something like that -- I am not fond of that word, but something that brings with it the notion of -- in a sense serving for everyone, yet serving primarily for the individual who would be the research subject to make certain that they have the translation as you aptly put it.

But also serving at some level in the research enterprise itself because imperfect understanding and imperfect participation increases the risk of imperfect results, people dropping out of the study, all kinds of problems down the road. So everyone, I think, has an investment or should in that process being as fully comprehensive and as well understood with as much dialogue as possible.

PROF. CHARO: Sure. The only reason I spoke about the loyalty being to the subject and not the research enterprise is that structurally -- we are going to be probably talking about this more explicitly later in the day -- every time somebody is formally associated with a research enterprise, and that is that their success or even their financial gain is measured by their ability to recruit people in, you find that there is now a fundamental conflict of interest.

This is one of the structural problems in the field that we have tackled imperfectly so far and that IRB's struggle with regularly. Although what I am talking about is something that might be totally

impossible to implement because of the sheet cost of it. I mean, large institutions might be able to have something akin to the patient advocate that we now have at our hospital who does this as a living. Right. And works with all sorts of subjects. Small institutions may find it completely unrealistic.

But still the notion that there is somebody who has not got the incentive to draw people in whose only measure of success is the satisfaction of human subjects as their involvement would be helpful in reestablishing a confidence in the process.

MS. FLYNN: Again, I think it is the kind of role that organizations that have enduring interests like mine does in seeing effective research conducted whether focused principally on the good and welfare of the individuals with the infliction can play an important role. I know there to be other groups across the biomedical arena that I think would welcome the opportunity on a voluntary basis to play that kind of role that are fundamentally supportive or and desiring to see difficult research continued to be conducted, but can play that translation role if you will with a fundamental connection to patient welfare.

DR. CASSELL: The American Heart Association has that group of volunteers.

PROF. CHARO: But, of course, there are going to be a lot of human subjects that are recruited for totally different reasons. For example, I was stopped during the break by a person who works here in genetics who said it might be worth putting on the table the distinction between well subjects and sick subjects because of the way in which they present.

You know, having been somebody who was the type of person who worked her way through college in part by being a well subject for an infinite number of experiments, I did not belong to a group that naturally would have this kind of -- college student government, but they are not worried about things like this.

MS. FLYNN: I doubt it.

PROF. CHARO: And I do not think I was seriously harmed, but I can count many times where I walked out quite surprised of the effects of having participated as opposed to what I had expected.

DR. CHILDRESS: One thing there -- we actually have a lot of topics to cover today, but compensation for participation research is an item that perhaps could use further guidance in the area of informed consent precisely because of the concern about what constitutes an undue inducement. So focusing on the possible compromising of the consent part. But the person now because of this incentive is induced to participate in research that he or she would otherwise have declined.

Is there anything we need to do on those lines in trying to develop -- and think about concrete steps we can take. We have had some very good proposals emerge already that are of a fairly general nature. We had a good debate about education versus facilitation. The process of facilitation -- on the process of consent/refusal. So each time I say consent I also mean the possibility of informed refusal as well.

But what else do we need to do? Do we need to say something or try to work on the area of developing some guidance?

DR. CASSELL: I need some enlightenment because a lot of the times when I -- well, this Eli Lily example that was put in front of us in

the Wall Street Journal piece. When somebody is offered money or when prisoners are offered inducements we say, well, that is unfair coercion. There is a certain paternalistic quality to that which troubles me. If I want to be coerced then I ought to be allowed to be coerced. So one of the --

DR. CHILDRESS: And coercion is not the best term here.

DR. CASSELL: Yes. What, in fact -- I mean, there are inducements always. There is nobody who is neutral in relationship to whatever is going on in the world. So I am somewhat troubled by what we mean by that.

DR. CHILDRESS: Well, that is one of the questions. That is the reason it comes up as an issue, is I think we are all troubled with that but there is no guidance available. Should we try to devise some there? Is this worth tackling as an issue as part of the informed consent process?

DR. CASSELL: I would have a lot of trouble getting through medical school now because they do not pay as much as they paid when I went through medical school.

(Laughter.)

DR. CASSELL: But I think it is something that we ought to discuss.

MS. FLYNN: Just to share on the one hand with mentally ill individuals there is concern that because they are generally an impoverished population that compensation may be seen as coercive. On the other hand I tend to share your view that it is precisely people who are impoverished who may perhaps really appreciate the resource that research participation brings them.

Interestingly, individuals who have participated in research who had a psychiatric diagnosis frequently talk about it in a different way. They will frequently talk about it as a respect for the importance of their contribution and see it as legitimate and will complain when such compensation is not built into research protocols because they see it as a disrespect for the significant role that they have been asked to play.

PROF. CHARO: You know, I -- this problem, of course, is just phenomenally deep because it goes into everything having to do with financial payments for anything, any risk taking operations or inducements to perform any number of services. It goes right to the heart of minimum wage.

I find myself wondering -- again it is a -- this is really a problem if you are an academic -- It seems to me that if you think about the way economists talk about the idealized market that you could look at experiments and say now which ones would people actually volunteer to do without any kind of compensation, whether it is financial or otherwise.

Because whatever people are volunteering to do, you have got to presume that that is essentially a market state just like my purchase of this coffee versus another, it is a market state. But it is worth to me and I am defining it as therefore worth it to me whether it is because of altruistic inclination, so it is a benefit to me to exercise my altruism, or it is because I actually feel like I might get some personal benefit out of the research which would be a way to define therapeutic totally from the subject point of view no matter how unrealistic. You know, for me .001 percent chance of cure is therapeutic. It is therapeutic for me.

Then separate out those where people would not volunteer

and then look at the phenomenon of inducements only at that point so it does not get totally wrapped up. Look at inducements of all sorts. There is the inducement of straight money. There is also inducements based on access to health care that you do not have access to otherwise. Not a rare phenomenon of people who want to enroll because now they are going to finally get a check up and they are going to get a diagnosis, and they are going to get a whole variety of other health resources that they cannot get otherwise because they are part of the uninsured poor or under served but insured poor.

Then it opens up the door to looking at other kinds of inducements that might not be used now but could become a new model of quid pro quos. Having served as a research subject I now become exempt from X number of months of national service or military service, or some other service that is associated with, you know, the general welfare. In some ways trying to separate out the inducement question from the underlying questions of the merits of the research might be useful in thinking through when it is abusive and when it is not, however we are going to define abusive.

DR. CASSELL: Well, it certainly does the raise the issue which I think your point was towards, is that it needs revisiting and that the automatic response is the ways that you use to encourage somebody is a kind of coercion just will not work anymore. It is not adequate anymore.

DR. CHILDRESS: And the poles of journalism and exploitation find a way --

DR. CASSELL: Yes.

DR. CHILDRESS: -- to avoid those kind of paternalistic

actions and also exploitative actions.

Okay. Any last comments you want to make on informed consent? I would like to move to the area that you excluded, vulnerable populations, and talk about children and impaired subjects.

DR. CASSELL: I would like to make -- maybe it is a transition comment. Somebody mentioned do not forget what happens with sick subjects. I have done a fair amount of work on thinking in sick people and there is no question that cognition changes in sickness and it does not change necessarily in people who are -- who fail a mental status exam -- when they pass mental status exams and yet be unable to take any perspective beyond the one they have at the moment.

And the easiest example is you can show some people who are sick but otherwise entirely competent by the usual cognitive capacity by the usual measures and do like a child's block A, B, C, D with one faced to them and say, "Do you see the letter A?" And then turn it around so they are now looking at the "C" and say, "What is on the opposite face?" They cannot tell you. It is not that they cannot tell you because they do not remember. They cannot tell you because they cannot decenter enough to see themselves as looking at that block from the opposite side.

When you see somebody do that who is otherwise perfectly competent it blows the mind except that that is -- you can understand that anybody else who gives you a perspective holds you in that perspective if you are sick enough. So that things look entirely reasonable from the perspective of the person advising you at that moment. You understand that this has to do with testamentary capacity and so forth. But it also has to do with the business of giving consent for treatment and giving consent

for research.

Once again there is no solution to the cognitive defect. It is there. And so any people who are sick may both have the defect and know they have the defect at the same time. Unlike the concrete child who does not know that there is -- that they have no perspective. But they can say I know I should be able to see it, but let me see if I can figure it out at the same time that they cannot, which could be also disturbing.

But the point is that they require some kind of help in being given back a perspective rather than being assumed that because they are an adult and whatever, and that they should have capacity they do. This is -- now -- then we understand when we get to the people of impaired capacity that their capacity is not just the capacity in the usual sense, but sickness itself is a kind of impaired capacity.

DR. CHILDRESS: Thanks for the translation.

PROF. CHARO: Jim, just a footnote I just want to put on your list for highlighting. Psychosocial and economic ramifications, screening patients, and how well they are being handled in terms of consent.

DR. CHILDRESS: Consent, yes. And there are others too --

PROF. CHARO: Yes.

DR. CHILDRESS: -- immunological studies with co-activities that change that.

PROF. CHARO: Right.

DR. CHILDRESS: Issues, too, that we need to keep in mind. Thanks.

As we look at an example of sick people as vulnerable

populations we are going to look specifically at children and cognitively impaired subjects. We will also talked briefly about other populations that could be included under that category and then selected these two in part because of concerns that have emerged in this area and in part because of special expertise and backgrounds of some of our subcommittee members. So concentrating here, but that is by no means to suggest that there are not others and we will want to look at those as well.

But the two areas of children and cognitively impaired subjects differ in that we are having to place regulations for children. The question is are the guidelines sufficiently clear to say in general carry minimal risk and minor increase over minimal risk, and further we need to propose some changes there. In the area of cognitively impaired subjects we have a lot more to do in the sense of a wide open area to offer some better reflection.

So let's start with the cognitively impaired, many of whom may well have been previously competent and able to exercise choices and may have actually exercised some choices regarding participation, and then move to children not having that capacity.

Laurie?

MS. FLYNN: I want to preface everything I have to say by repeating that I am not a scholar, not an expert, not generally one who dwells in these realms, and so I will offer some comments more in the spirit of reflections and concerns from the community of individuals and their families who are concerned with this. I will raise questions, not so much solutions, and try to bring some sense of the areas in which we might most fruitfully focus our attention.

As you suggested, Jim, it is important to distinguish, at least with regard to psychiatric illness, the difference between cognitive impairment that we may see with children or the recognition that children are vulnerable because of their developmental status and the cognitive impairment that we see with respect to many forms of mental retardation.

With children we are seeing an increasing developmental capacity moving from infancy towards adulthood. We, therefore, can titrate the degree to which their participation enriches part of our thinking. With mental retardation in many cases we can reasonably well measure and move forward with a stable sense of what the capacity and, therefore, involvement can fruitfully be.

With psychiatric illness we have instead something that is often quite exotic. The impairments are much more difficult to measure becasue they are not necessarily stable over time. It is a matter of conjecture, you know, at what point have we achieved a sense that there is competency to consent. We do not really have any standards broadly utilized and agreed upon that would measure that capacity. Yet it is essential to the issues that were just addressed around informed consent.

There is some particularities also to know about serious psychiatric disorders. They are like all disorders. They range from mild to quite severe. So that simply having the psychiatric disorder labeled does not automatically imply anything in particular about one's ability to participate in research, understand and consent fully, and participate fully. This is not a homogeneous population. Even the very severe diagnoses vary considerably in terms of their impact on individuals.

It is also important to know that judgment is, indeed,

characteristically impaired at least during severe episodes of psychosis or depression, that cognition is, indeed, impaired during episodes of psychosis or depression, and in fact in some situations not only does the disorder over time accrue disability that may leave real residual impairment even after the episode itself has been resolved, but there is some evidence that even some treatment can as part of the risk/benefit ratio that one participates in leave the individual with some potential impairments in their general ability to participate effectively.

So it is a complex set of disorders and the impairment are both real and sometimes subtle. They are highly variable both to individuals and through the course of the lifetime of illness.

Also characteristic of these illnesses, particularly those that feature psychotic episodes, is a frequent denial of illness at all. A frequent assertion that there is really nothing wrong, making it again difficult to know when you are trying to engage individuals and frequently you want to be engaging individuals who are in the throes of their disorder, making this a very challenging area and certainly the research is very difficult to adequately meet all of the kinds of ethical tests that we would like to see.

People with severe and persistent mental illnesses are typically a very vulnerable population if their illness persists. Formerly, as we all know, they have spent lifetimes in institutions and they are a ready research population. Clearly there has been a history and recognition that there have been some abuses and there is a sensitivity in the patient community in particular to being certain that given the characteristics of their disorders and given the history of a perhaps lack of respect for their capacity there is a particular sensitivity around being active participants.

Many research subjects I think across the board, and I think this is clearly true particularly of those who are perhaps also characterized by poverty as many of our folks are, tend to believe that research and everything we have discussed today actually equals the best possible treatment. That if you can get involved in a research protocol you will get the best possible treatment. Given the nature of many of these psychiatric medication studies in particular it is very important that we pay attention to the fact that that is not necessarily true.

There is, I think, often a surprise both for families of research participants and the participants themselves when they find out that they may very well be assigned to a group that is in a sector that is not going to be receiving any treatment or only minimal treatment, and certainly may not be receiving the new and potentially more efficacious treatment.

This is a particular problem for people with severe mental illnesses because most of them are impoverished after three, five years of illness. They have run out of any private insurance if they had it. They are now reliant upon Medicaid. They are reliant upon the public mental health sector with its well documented deficiencies. So they are particularly eager to participate in any kind of clinical research that may really offer them literally any access to treatment that they can find or the only access to improved treatment.

We certainly see and hear within our own organization constant searching amongst families for where these kinds of clinical trials are going on, how they can possibly get their relative enrolled, and there -- one needs to always be aware that there is a very strong incentive pushing

people in the direction of these trials even though we know that they may or may not actually receive the treatment and the protocol may not allow them to have access to the newer medication or newer treatment that they may be seeking.

The subjects of these clinical trials and other psychiatric research are, as I mentioned, difficult to recruit, difficult to retain, and to the degree that we want to focus typically on the more severe illnesses we face even greater barriers and hurdles to bringing folks into various research settings.

It is important to recognize their vulnerability not only in terms of the cognitive impairments, but approximately 15 to 20 percent of individuals with a severe psychiatric illness will complete a suicide over the course of their career.

DR. CASSELL: What percent?

MS. FLYNN: Fifteen to 20 percent will complete a suicide. And they die on average 12 years earlier than their age matched cohort. So there is a vulnerability that goes on beyond the obvious kinds of impairment that we need to be aware of.

Families in the deinstitutionalization era bear a particular care giving burden and families are very concerned that they have not been effectively incorporated into research design, development of research protocols, and the informed consent, and ongoing consent process itself. As I indicated earlier, particularly for a population that has some cognitive impairments and may have episodically great difficulty seeing consent and participation as an ongoing educational process. It is crucial and yet it is still at least in my experience talking with folks the exception and not the

rule.

There is a great desire on the part of may to supplement these processes by implementing a system whereby the individual who is to be the subject of a research is accompanied by a family member or a close friend as the informed consent procedure is undertaken. Somewhat to serve in a kind of translational role that Alta talked about as well to ensure that given the family's ongoing care giving role and given the fact that most of our psychiatric research today is occurring in the communities rather than in an institutional setting, giving someone else some information who can be a support and back up and early warning system because these are subjects who can rapidly decompensate and deteriorate.

Lots of folks have also said to me that they worry a little bit about having the informed consent process undertaken directly by -- and again as Alta mentioned -- the principal investigator or individuals who have a direct stake in getting those numbers completed. That they would like to see both the opportunity for the principal investigator or someone who is formulating the research design and responsible for it available to answer questions and explain what is going on, but that someone not directly interested might better be engaged in actually walking through the stages of making certain that the individual understands fully, has the opportunity to ask questions, and clearly give appropriate consent.

So again I think we need to be looking at these issues.

DR. CASSELL: Could you enlarge that? Why they want to do that and so forth.

MS. FLYNN: Well, because of the -- (A) the great desire and difficulty to get these subjects into research, the difficulty in being certain

that one has been able with more impaired subjects to achieve effective consent, just a sense that there is also such a desire to get accepted into these studies, such a desire to become -- to have access to this potentially beneficial treatment, that the whole process may be somewhat compromised. That there is sort of everybody wants to collude to saying yes and that there may be less of a fully objective, extensive discussion and assessment of whether or not informed participation has really been effectively gained.

I think that the stakes rise as the research contains greater than minimal risk, as the subject presents a greater degree of impairment. But again I bring it to you because it is an issue that is talked about and it is an issue of some concern, and one is always looking for, you know, ways to move forward the discussion.

As I indicated earlier, there is a tremendous concern about the lack of real partnership with the patient and family community in the design of these protocols, in thinking about the questions to be addressed, in looking at ways to improve the way in which the research is undertaken, and as has been mentioned almost never does anyone hear anything about what was learned as a result of the research. So that the sense of being a valuable participant who shares in the development of new knowledge really is not afforded to many people who participate. I think that is an important problem.

We have talked a little bit about the need for training, the need to train not only investigators, but we find tremendous concerns about the level of training of the IRB's. Participation on the IRB's generally does not seem to be drawn from our community at least and we would

intend to see situations where if the IRB looks a lot of research with these subjects that there ought to be a member from that community as part of the IRB, that there ought to be available consultation from that community to assist the IRB as it reviews and tries to arrive at acceptable research protocols.

There are a couple of really difficult issues that have not been talked about but that certainly bear in our community. One we have touched on is what is the impact and what do we know about the growing trend of industry sponsored research? There is a great deal of this in our arena. It has -- it holds great promise in the sense that we are in the middle of an enormous explosion of new and better therapeutic agents for these disorders. But much of this research is conducted outside the Common Rule or at least it can be.

We know very, very little about what kinds of safeguards and procedures are in place. We have some concern about the insularity with which that research seems to be conducted and believe that a dialogue with industry around this and some ability to try to expand the parameters if you will given that so much of that research is important is now outside the realm of what we typically are looking at.

The Office of Protection from Research Risks seems to us to have very little ability based on its current structure and budget to do the kind of ongoing monitoring that those of us concerned about cognitive impaired subjects would like to see. I do not know what the right number and what the right balance is, but it is troubling that even with longitudinal studies, which are critical for this population, there is very little ability really to make site visits to get interim kinds of reports.

I think that particularly around subjects that are viewed as vulnerable we need to give OPRR a mandate to do more there and perhaps require some more frequent reporting, and to see a greater oversight role with studies that are either at higher risk or studies of longer tenure where I think there is a tendency to get approval and then it sort of runs on for the next five years and nobody kind of looks at it again.

We wonder if there is not some value given that there are a lot of studies going on with impaired subjects and vulnerable populations of creating some mechanisms for sharing of information from IRB to IRB. Each one seems to reinvent the wheel and deal with protocol de novo each time. It occurred to me after the experience I was telling you about earlier that the local IRB and the sort of practical, specific suggestions we made about their outpatient monitoring was quite insufficient in our view.

Once a week kind of check in was not nearly good enough for folks who were going to be going through a drug washout and we told them we thought three times a week would be important, declining to two after a period as they moved on to the experimental drug. We told them a 24-hour kind of crisis line where individuals could call if they were in need and that that number ought to be given to family and care giver should there be a rapid deterioration. Very practical, implementable suggestions.

And then you think to yourself this kind of conversation may be taking place in lots and lots of IRB's only they may not have someone with the kind of practical experience sharing it. So you wonder if there is not a way to facilitate particularly around greater than minimal risk studies and particularly around vulnerable populations or other populations of special need.

Some way to share this information so that as wisdom improves about what seems to be working well, what can in fact be implemented effectively, what does the community believe would be adequate safeguard, so the sum of that knowledge can be more uniformly shared. I believe there is a desire for it and I think that there would be some real help offered if we had a way to do that.

An ongoing issue of some real concern that was touched on earlier that is specific to cognitively impaired individuals is a problem of placebo controlled studies and not just a drug washout period, but the ongoing ethics of placebo controlled trials for individuals who have major mental disorders.

The problems as we try to listen -- we talk to the investigators and say why do you continue to believe these to be the only way these studies can be done. Can't we simply compare the new medication against standard treatment? Typically their response is, "Well, the drug companies will not let us do that." The drug company insists on a placebo controlled trial. So when you talk to the drug company and ask them why are we studying against placebo, why can't we for some of these well established drugs work against the standard, and they will say, "Well, the FDA requires it."

So there is a kind of buck passing that goes on about why we continue to see at a time when we really understand not only the short term dangers for individuals with severe disorders who are assigned to the placebo, but we also understand longer term dangers. Short term dangers periodically are documented as suicide, violence. There is also less well documented as estrangement from family which may be the safety net for

the individual. The loss of Medicaid benefits, homelessness that could potential result.

People decompensate rapidly and people can lose everything in a short period of time, particularly in outpatient settings where they may be out of touch with or lost to follow up. There is a readiness to kind of -- they dropped them from the study because they do not participate but, you know, there is a responsibility to these individuals that seems to me goes beyond simply noting that we have lost one to the study. We may have lost one in many other ways.

But there is also considerable evidence that each time there is a breakdown, a relapse, that there is accrual of disability. That in other words individuals do not return to baseline functioning once the episode is resolved. So that there really are substantial risks beyond the obvious ones for individuals who participate in these studies and it is of some concern that there appears to be very little questioning of their ongoing significant importance.

So I wanted to raise it because I think it is something we ought to look at. Is this still necessary? Can we not answer some of the questions we have for some of these subjects that have so much to lose? Whose responsibility is it really to let us know that as with other significant life threatening disorders we only need to demonstrate efficacy against standard therapy rather than against placebo. So that is an ongoing controversy that I think we need to recognize.

Another area is the difficulty in having effective safeguards around the research that is needed on those who are most impaired. At some level it is easier to study those who are less impaired, who are more

stable, and yet it is research on those whose disorders are least well handled that is actually most necessary. I think that is a difficult dilemma but I would want to encourage us finding ways to satisfy ourselves that we have safeguards and not limit the numbers of individuals who can successfully participate even though they may have significant problems with their disorder.

Two other things that surround this issue that others may not be aware of but that are important as we think about what we write and what we do and how we focus the issue. One is the reality of the particular stigma that attaches to mental disorders, mental illnesses in particular. This is real. This is ongoing. It adds to the burden of psychiatric research. It adds to the burden of the individuals who participate in research. Many of them have told me that participating in research actually enhances their self-esteem. It is an important way to participate effectively and to combat disorders that are often tremendously devastating.

The other thing to know that there is alive and well a very vigorous and vocal antipsychiatry movement of former patients who may or may not have been effectively treated or abused in research. Some of them have apparently not even been accurately diagnosed but they are very vocal and they color the political environment in this research is undertaken, an environment which is difficult to begin with.

Then there is the reality of scientology, which has made psychiatric research a specific particular target. There are almost no major research centers that are involved in studies of severe psychiatric illness that have not had one or more very unpleasant confrontations with the Church of Scientology.

Subsequently having been named to this panel I have had several what can only be characterized as hate voice mails left at my office for me. The Church of Scientology has long sought to discredit psychiatry and psychiatric research and again it means that we need -- all of us need to take particular levels of care as we think about where reforms are needed, where revisions are needed, where reaffirmations are important.

While I would always come down on the side of safeguarding and protecting patients, we also need to know we have a somewhat more vulnerable than ordinary research enterprise here. So the balance would be important to strike.

DR. CHILDRESS: Thanks for providing that important full review of the range of issues that arise particularly in this area.

In the package we had proposals from a variety of people. Rebecca Dresser, for example, but then also the Maryland State proposal to develop guidelines with regard to the cognitively impaired. And then as part of the informed consent discussion, which has taken place at the Center for Biomedical Ethics at the University of Pennsylvania, we have a draft in our packet which also then has an extension to the cognitively impaired. So it is an area that is receiving a lot of attention. In part, as Dresser and others have noted, because there is so little guidance in this particular area.

You have given us a variety of reasons why. At least at certain points we ought to think about further guidance. The difficulty is going to be trying to work that out. But in this area, as in so many others, there is a lot of work going on that we could build on and would not have to view this simply as starting over again.

Let's take a few comments about this and I would like to get the discussion of the children started before lunch simply because I am conscious of the time and we need to go to lunch as close to 12:00 as possible in order to avoid the crowds.

Eric?

DR. CASSELL: Well, Laurie, I think that was wonderful. It comes down once again to the phenomenon that is so common among physicians of not having any idea of what it is like to be sick. Of investigators and psychiatrists who really do not know what it is like to be a sick person in the population that they take care of every day because -- well, for obvious reasons. But -- and that there is no substitute for that knowledge.

The example you gave of what happens in a placebo controlled trial when that brings somebody out of their control -- I mean, the previous control over their lives and then they are gone. A danger that is not listed in that informed consent, I am sure, you may lose your Medicaid, you may lose your so forth and so on, that is not listed in that informed consent.

MS. FLYNN: Right.

DR. CASSELL: And but it brings us once again back to the nature of the relationship between the investigator and the subject. When the investigator is more intimately related to the subject and what happens to the subject then these things are better avoided than others. That is on the first thing.

The second thing is as everybody is passing the buck they may absolutely be right. We have a representative of the FDA here. Do we,

Jim?

DR. CHILDRESS: We did earlier.

DR. CASSELL: Yes.

PROF. CHARO: All eyes.

DR. CASSELL: In fact, if the FDA does require a placebo control for this kind of thing that is something that could be addressed and if they do not that is something to be addressed on the other end. I mean, there are matters of substance in these too. You know, lots of some things are solved -- you know, as we say, some things are solved by taking some pain medication. Some things are solved by changing a requirement.

DR. CHILDRESS: Any response? FDA?

DR. _____: (Not at microphone.) I am not in a reviewing position.

DR. CHILDRESS: Okay.

DR. CASSELL: You are not in the right division. Not on my shift. We call that not on my shift.

DR. _____: (Not at microphone.) Well, if it happened at midnight and you were on at 12:00 noon, you are right.

DR. CASSELL: Yes, not on my shift. We understand that.

DR. NORTON: I am Amanda Norton and I am in the Office of the Commissioner as Chief Mediator and Ombudsman. I will offer you what I know about this with the caveat --

REPORTER: Excuse me. Could you come toward the table?

DR. NORTON: Oh, sure.

REPORTER: Thank you.

DR. NORTON: I am Amanda Peters -- I am Amanda Norton.

Excuse me, I just changed my name.

(Laughter.)

DR. NORTON: And I am in the Office of the Commissioner, Chief Mediator and Ombudsman. I will offer to you what I know with the caveat that the Center for Drugs will have to supplement, but just for today's -- because I was talking to one of the senior folks at the Center for Drugs about this very issue briefly a time ago.

That is that trials in these agents are very, very difficult to prove efficacy and that there will be lots and lots of trials, and many of the agents that have shown to be effective in certain patient populations have also demonstrated no difference from placebo in many, many trials.

So I think there is a real issue here that needs to be looked at and possibly -- and I am sure FDA would be happy to be involved with this thing. Maybe there are ways to tease out areas where we really do know that standard therapy works under certain circumstances.

But I think it is really the difficulty of measuring efficacy that has led FDA to maintain the desire to have a placebo control as opposed to an active control. But it is a very complicated area. This is what -- I was inquiring about the same subject.

DR. CASSELL: Well, the desire to have and the requirement for are not the same thing.

DR. NORTON: Well, the agency by law has to be satisfied that there is adequate safety and efficacy to the drug to approve it. And so, you know, how that comes about is a difficult question and I think it is an important one in the context of what is being discussed here because I think the experience, and the agency's experts can certainly fill this in, is

that it is very hard to demonstrate efficacy. And some of the very valuable agents that do help people with disorders, in fact, do have a very checkered history.

So the agency -- you know, I am sure it has made lots of changes in recent times to respond to various patient groups and new information. This may be an area where it is time for another look. I do not happen to know whether there has been a recent second look or whether there are particular areas where this problem can be addressed or ameliorated, or at least explained to greater satisfaction so everybody understands what is going on.

DR. CHILDRESS: Thanks very much. I will take one more comment on this area. We will have to come back this afternoon and decide basically between two and three, is decide what kinds of -- what we want to focus on first and this is one area that a lot could be done in and a lot is already happening, but one that may need our attention fairly soon.

But any quick comment?

PROF. CHARO: Yes. Again an inquiry to get a handle on how serious certain aspects of the problem are. Except for the Maryland recommendation, most of the stuff I have seen has said that at a certain point where the risks are more than just a minor increase over minimal risk, and there is no necessary anticipation of benefit, which I think is a familiar phenomenon in this area, is variability of treatment.

That basically third parties really should not be privileged to give consent on behalf of the person with the mental illness, right. So I am focusing now only on people who are not competent or not going to be continuously competent, and for whom therefore there is a third party

involved.

And, thereby, we exclude from the arena of research those things that would have to be tested on these kinds of people, people who for example are recalcitrant to standard therapy, and they have third parties.

What I am trying understand because I note this and I noted a similar problem with children, I would like to understand better if you happen to know the degree to which that poses a genuine problem in the advancement in this area or whether that encompasses a very minor area of research so that we can safely just say, all right, well, let's not tackle that one yet?

MS. FLYNN: I wish I could give you an answer and I will -- I believe I could get one for you fairly quickly.

PROF. CHARO: Okay.

MS. FLYNN: It is a concern to me and I tried to allude to it in my comments that it is this most recalcitrant treatment refractory, difficult to engage, oftentimes these are individuals who may have a history as well of substance or alcohol abuse, self-medication if you will, that present some of the most difficult problems. And yet if we could get a handle on better treatment and better response to these individuals we would do a good thing.

So I do not know whether the research community has found some ways to deal with it. I am aware of fairly strict protocols that seem to rule out many of the very people who we most need to get a handle on. That is the anecdotal response I can give you.

PROF. CHARO: Right.

MS. FLYNN: How they are coping with it or if there is no great desire to move in that direction because we have no great hypotheses to test in that direction, I do not know, but I will find out. I will ask.

PROF. CHARO: Thanks.

DR. CHILDRESS: Would fifteen minutes be enough to get us started?

DR. BRITO: Yes.

DR. CHILDRESS: All right.

DR. BRITO: A lot of the same issues that Laurie so well and thoroughly discuss also pertain to children, but particularly in the areas of vulnerability, impoverishment and accessibility issues for the cognitive impaired also apply to children everywhere. This country, of course, being included in that.

Children are one of the many vulnerable groups which -- you know, I have put a lot of thought in this, what is vulnerability and how you define it. And I define it as anyone that is in a potential -- in a situation that is potentially set up for abuse by someone in a position of power and this can be because of economical differences, educational, cognitive, physical, political or even geographical differences. In other words, areas where someone is set up not to get appropriate health care and has limited options because they live in an area that is not accessible.

So I think when we think about children and the cognitively impaired as two of the vulnerable groups we need to think of everyone, and we are all vulnerable at one time or another when you think of vulnerable groups and of people having more similarities than differences. But there are some unique situations that children are in.

They are vulnerable because they are at the mercy of their legal guardian. And while we all would like to think or we -- maybe not all of us think this way, but we would all like to think that the legal guardian or the parent, or grandparent, or foster parent of the child is looking out for the best interests of that child. My experience as a clinician has shown me that that is not always the case.

Even though it is in the minority these are the children that are the most vulnerable, the ones where the parent or guardian is not looking out for the best interest because of economical reasons, because of cognitive problems that that parent may have, or that parent may be cognitively impaired themselves. So of course there is other mental illnesses, et cetera, that I will not get into the details of but they could all influence that.

So this is where children are a little more vulnerable than others. Sometimes there is a secondary gain to having a sick child in the medical field and that is also a set up for vulnerability.

So my major questions when I am thinking about children as well as research subjects are how can a child consent for something he or she does not comprehend or at least comprehend in the same way that an adult does? And, of course, at different ages children comprehend different things.

How can we determine if the person looking out for what we believe to be are the best interests of that child, how can we determine if they truly are looking out for the best interest of that child?

And Alta's earlier discussion of the exclusionary problems certainly applies to children. There are clinical trials that may be beneficial

to children that lag in the research efforts because of -- sometimes of what can be overly protective measures.

For instance, the example in clinical AIDS trials. The AIDS groups have been as we all know very powerful, very powerful in pushing for clinical -- trials of drugs in adult patients, but in children there has been a lag of a few years until we are sure that they are -- certain medications are effective in adults we are not going to try them in children. Then there is the issue of numbers, et cetera.

So the point is the FDA has not approved a lot of the same medications for children even though as a clinician sometimes I know in speaking with some of the infectious disease experts in this area that these medications would most probably work in children. The point is that the children do not have a voice like the adults do in these trials. So sometimes we need to be careful not to be exclusionary when we make recommendations for consent for our research participation.

The last main question is when does investigations in children benefit the community and when does that benefit outweigh the risk to that child? Okay.

It all really goes back for me to the informed consent issue. I think when we think of children we need to think of them as one of many vulnerable groups and I think when we discuss what there is we can do to improve the adherence to previous recommendations for consent we need to look at what those areas that have not been adhered to or what the misunderstandings, or what the difficulties have been with consent, and how do we measure the importance of research in a community, its benefits to people overall, and how they outweigh or may outweigh risk to

individuals.

My suggestions basically are for encouragement for more research are needed in the area of the consent issue. We need to, like Laurie mentioned, we need to have ongoing monitoring to increase adherence to consent.

But we need to have the consent forms be more of a partnership where in the situation with children we somehow develop a system where the person, the investigator, somehow assures us -- us being the review committee, us being the community that is looking at these consents, us being the IRB's -- assure us that the person looking out for that child is truly looking out in the best interests of that subject and they are capable of making decisions for that child.

That that person has the cognitive ability to understand the pertinent issues and if they do not have the cognitive ability then some means of helping that person to understand better what the issue is and what is involved in a child being involved in a research program.

So basically we need to devise specific measures to have broad applicability in terms of consent that are going to apply children, apply to cognitively impaired, and other vulnerable groups.

DR. CHILDRESS: Thanks. Let's have some responses to these proposals and other things that have been offered, for example Loretta's compliment discussion and others we had in the -- Ross and others in the packet.

MS. FLYNN: I would ask the same question about children that Alta was asking me. Do we see a lack of research in areas that we would see as important? Do we find that there are currently insufficient

safeguards or too great barriers to participation so that this is an area that would need some attention rapidly?

DR. BRITO: Absolutely. I think there is a lag time in research in children in many areas. Actually one of the exceptions, interestingly developed by the oncologists earlier on, is in oncology where there does not seem to be as big of lag time and I am not really sure why that is. Maybe one of the oncologists here could help us with that.

But there are many areas and AIDS is the perfect example right now. The other one is mental health in children themselves. Why there is such a big lag in intervening early on, et cetera. A lot of it comes down to financial or economical reasons.

MS. FLYNN: There is also in mental health the same issue you raised in the AIDS, an understanding on the part of clinicians that many of the medications could be appropriately used with youngsters but lack of research, lack of data, lack of indication that would permit comfort in prescribing.

PROF. CHARO: Can I ask just to pursue perhaps some of the economic forces that are driving some of these and the way in which they interact with the regulatory system? Focusing just on drugs for the moment because I think the drug and device area and FDA's intervention is distinctly different.

I was under the impression that because of the way we constructed children as a vulnerable population that it is expected that one begins with adults and after having proved safety and efficacy in adults one then might turn attention to children.

But that if you have a drug that has been approved for

adults and is now marketable, but there is very little incentive for a company to now pursue research on children for safety, efficacy and dosing because the drug can prescribed off label by any physician. In other words, you can have massive individualized experimentation without the usual routine.

Furthermore, that any company that wanted to do the investment for an R&D to get a specific labeling change approved by FDA for indications in children would have been forking out the money on behalf of every other company that has now been manufacturing the same drug, that the patent has now expired because that labeling will be available generically.

I also understood that this seemed a problem that transcends children but it is just a problem in general with supplemental IND's that is now the subject of debate within Congress and FDA about new incentives for supplemental IND's that might tackle some of these problems since it is at the behest of the license owner or manufacturer to initiate the research.

I would be interested in knowing about where those things are going to know whether or not this problem is going to be tackled already because of the supplemental IND problem or is it time to be thinking about where else could you put some kind of mandate for such research in place since the private sector will never have the economic incentive to pursue it.

(Simultaneous discussion.)

PROF. CHARO: I would love to know why the private sector has pursued it in the areas you have identified to maybe understand what

is different about those areas than the general --

DR. BRITO: One other quick issue regarding that is that when the private sector has pursued in poor populations, children, cognitively impaired, it seems like they pursue it only to the point where there is -- this is my general impression -- is there is a benefit. Unless that benefit is known it is withdrawn from those populations and not necessarily applied to those populations.

DR. CASSELL: Say that again.

DR. BRITO: In other words, if there is --

DR. CASSELL: It is only used in that population until a benefit is seen and then the drug is not offered --

DR. BRITO: Right. People -- for example, someone without health care may be involved in a research study, placebo versus control, et cetera, and they may receive that during the trials. But once that is withdrawn -- once a trial is over there is no guarantee that there will be ongoing therapy for that patient even though there have been benefits proven for that.

MS. FLYNN: That is important for our folks too and that is an area I actually failed to mention. But it is very troubling.

DR. BRITO: Continuity.

MS. FLYNN: The continuity of care. But because we are recruiting among vulnerable populations, because they are often impoverished just as you say and there will be some response and they will do better on the experimental protocol, and then the design is finished, the experiment is over, and in too many cases access to the medication is withdrawn, which strikes us as not appropriate.

DR. CHILDRESS: Any other --

DR. BRITO: Unethical.

MS. FLYNN: Unethical.

DR. LEVINSON: I think there is an additional issue. What you say is absolutely true but I have heard -- in fact, the FDA -- current FDA Commissioner is a pediatrician and he is particularly concerned about some of these issues because as he sees it children are not small adults and their reactions to particular drugs are not necessarily going to be the same.

So that there is a danger in prescribing for them drugs that have been approved and tested only in adults. But that with children there is an additional liability concern that provides a disincentive to the drug companies to get into that particular --

PROF. CHARO: Right. Because of the inadequacy of third party consent and an obstacle --

DR. LEVINSON: Right.

PROF. CHARO: -- to becoming financially responsible for long-term injury.

DR. LEVINSON: And people also see that and an additional danger in looking in children because people feel that with the longer expected life that there is an additional financial risk --

PROF. CHARO: Right.

(Simultaneous discussion.)

DR. LEVINSON: That is exactly right.

PROF. CHARO: But still, you know, with the pediatric population being constantly replenished, right, you would think that there

would be more --

(Simultaneous discussion.)

PROF. CHARO: We were reminded to think about future generations earlier. You would think that for a large number of indications the predicted market would be sufficient that if the financial incentives were in place it would still be cost effective for private sector entities to pursue the R&D.

DR. LEVINSON: Only when the risk/benefit -- for example, in oncology it gives you that because --

PROF. CHARO: Right. Exactly.

DR. LEVINSON: -- because the risk or the potential benefit is such that they are willing --

PROF. CHARO: Right. This is what I am trying to get a handle on, is where we have already seen that risk/benefit point passed and what the effect would be of the kind of generic solutions about the disincentives to pursuing supplemental labeling from FDA would handle the problem and then figure out what is remaining that would not happen if you had the children --

DR. LEVINSON: Lethal diseases. Cancer and AIDS, and then you back off from there. Gene therapy, we start out with a lethal disease and then you -- where the risk/benefit ratio is conducive to undertaking that experiment.

DR. CHILDRESS: We will take a couple of responses here before closing. Yes, identify yourself, please.

DR. WILSON: I am Ron Wilson of FDA. Dr. Friedman at the agency has been heading up a working group on looking at the problems of

supplement indications. He indicated last week at the Food and Drug Institute annual meeting that the group is expected to put out their recommendations or some items for discussion as a result of their working group. He was sort of asked specifically when they were expected to come out with some of the ideas for resolving some of these problems. He said within about two months.

Also something else, you were talking about the placebo control trials. We do have an information sheet at FDA that goes over these issues.

The placebo control trial is a very complex subject. But there are some papers that we have put out at FDA that provide information in this area. If you would like I could get it together and provide it to the members of the committee.

DR. CHILDRESS: Would you, please? Thank you very much.

We will make this the last comment before lunch.

DR. NORTON: (Not at microphone.) I just wanted to remind you --

REPORTER: I am sorry. Could you stand up or speak up?

DR. NORTON: Right. I just wanted to remind you especially with respect to supplemental IND's in oncology I would say for most of the commonly used effective drugs there has never been supplemental IND's and the labels have never been changed. The drugs are simply used.

PROF. CHARO: Right.

DR. NORTON: And the research goes on. It is in the journals and, in fact, all the insurers have to pay. There are laws now in the states in place that say even if it is not on the label, if it is in this and this

and this peer reviewed journal you still have to reimburse. So if the need is there they do not need the supplemental IND and I am sure there is financial needs. But of course again it is the issue of what happens in a very serious disease. It changes the rules.

PROF. CHARO: So in that middle ground of less serious, but nonetheless serious diseases, the insurers will not pay unless either there is an indication on the label or there is a state mandate that they must pay despite the lack of the indication?

DR. NORTON: That is right. Well, at least in some states. I know from the state I came from that Blue Cross/Blue Shield stood up and said we are not going to pay unless it is on the label.

Well, for many cancer drugs, 90 percent of what it is used for is not on the label. So the state legislature stepped in very quickly and said, "No, you are not, you are paying. If it meets these criteria you pay." Stepped right in.

DR. CHILDRESS: Thanks. Do you want a final comment?

DR. BRITO: Yes.

DR. CHILDRESS: We will pick it up again after lunch.

DR. BRITO: It is just interesting that in my own conversation and discussion we began the conversation about protecting human subjects in research. The subject of children and in a lot of ways cognitively adults has shifted from inclusionary problems to exclusionary problems. So that is just something that -- food for thought.

DR. CHILDRESS: All right. Let me remind the members of the public if you want to participate in the public comment period please check with Pat Norris and sign up.

We will pick up with the discussion of children after the lunch break. We will talk briefly about other vulnerable populations. We need to talk about IRB's and compensation for research related injuries, and a few other matters before we concentrate between two and three on basically deciding how we are going to pursue our work.

Bill, any comments you or Rachel would like to make before we break?

Okay. Be back at 1:00 o'clock.

(Whereupon, luncheon break at 12:05 p.m.)

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

(1:10 p.m.)

DISCUSSION BY SUBCOMMITTEE MEMBERS CONTINUES

DR. CHILDRESS: All right. Let's start. We have a fairly tight schedule this afternoon.

An article appeared today, a letter to the editor in the Wall Street Journals focused on the clinic. Let me circulate that.

We will take a few other points on children before we turn to other vulnerable populations and then to IRB's and compensation. Again, around 2:00 we would like to turn to the subcommittee deliberations about priorities. I hope it is not all of the above or at least not all of the above immediately.

One of the issues you raised, the third one you raised I recall, Arturo, focused on issues of risk/benefit analysis. And one of the major concerns expressed about research involving human subjects, particularly about IRB's and about variability among IRBs, is how one understands minimal risk, how one understands a minor increase over minimal risk and so forth.

This is an area where there remains a great deal of uncertainty. I am not sure how much light we would be able to shed on it but it seemed like one we probably need to address. It certainly relates to your third question and concern.

Any other comments about children as research subjects?

Alta?

PROF. CHARO: One other. In part because I had a chance to talk with Kathi Hanna over lunch. Kathi, by the way, is a policy

consultant and is sitting at the table. Kathi and I were talking about the discussions this morning and she had noted in her experience with NCI how that is a population which -- what did you say, 85 percent of the children who are given pediatric oncology treatment are getting it under clinical --

DR. HANNA: Are on a clinical trial.

PROF. CHARO: Are on a clinical trial and that for those that are getting treatment outside of clinical trials the treatments extraordinarily successful in part because of the phenomenon of extensive use of clinical trials for the kinds of reasons that Laurie was talking about in terms of parents and in Laurie's case third parties of various sorts wanting desperately to look for solutions in an area that is clearly not filled with adequate solutions.

So it made me wonder again about the kind of thinking we have here about who is not yet getting something in the context of children. We were talking a little bit about the fact that serious diseases may be adequately covered now in some intermediate ground, but I would just love to put it on the table for an agenda item.

Better capture. What population of children are either being abused or not getting something that they ought to be getting or what kinds of services are not being adequately tested so that they can go out into the child population. I am still unsure.

DR. CHILDRESS: Okay. Any other points?

MR. DOMMEL: And there has been -- I had mentioned to Jim earlier the NICHD and the Office of Extramural Research at NIH has been exploring enhancing the involvement of children in research. I think they have an internal report. So at lunch I went over to Dwayne Alexander's

office, Director of NICHD, to see if I could get it and he was away. But I will follow up with that.

PROF. CHARO: Great. Thank you.

DR. CHILDRESS: Thank you.

MS. FLYNN: This is perhaps slightly off the point but it was raised with me to bring here. There has been from time to time reports -- there have been from time to time reports of the inadequacy of administration of pain medication for adults. And periodically we hear about everything from end of life discussions to post operative recovery and so on.

I wonder what is known or if there is information about the adequacy of pain relief for infants and children who are involved in a variety of clinical settings. It may be that there is data and you can produce it, and that is fine. But I was asked to raise that issue by folks who believe that perhaps we have not paid sufficient attention to it.

DR. CASSELL: Well, it is just -- I saw an experiment done just in the literature in the last -- in the last few years that, in fact, infants have pain and require analgesics.

MS. FLYNN: Right.

DR. CASSELL: So we are not talking about adequate pain relief, we are talking about the conception that the infants have pain.

MS. FLYNN: Right.

DR. CASSELL: Now pain is not my perception. My perception is that mechanism by which you are aware of obnoxious stimuli. Pain is the perception of and pain always has a subjective element, and part of that thing is that infants have lest subjectivity when they perfectly

clearly do. They are interacting with their parents already and yet they were considered not to have pain. It is my impression also that children do not receive adequate pain relief although they tolerate analgesics better than adults do.

MS. FLYNN: Than adults, right.

DR. CHILDRESS: Okay. Any last point on children?

What other vulnerable populations? One, obviously we talked about women and their greater inclusion in clinical trials and other research context. But a subset of women, pregnant women, I guess clearly remains a controversial area and some proposals have emerged, but nothing yet has been formalized. Is that correct?

MR. DOMMEL: Right. A Public Health Service work group which I chaired when I was with the Office of Protection of Human Research Risks, with representatives from throughout the Public Health Service, reviewed the subpart that protects women and fetuses, and addresses in vitro fertilization for just about a year and developed a proposed regulation which has been forwarded to the Department of Health and Human Services for consideration for publication by the Secretary as a proposed rule.

The major issues addressed there, whether to the extent necessary or not would be subject to public comment, would be requirements for paternal consent in some circumstances. A requirement that for pregnant women to be involved in research she must be competent and that research which would unduly place -- and that research which might place at risk a fetus but which would provide no benefit for the mother might not be able to be carried out depending on the level of risk.

So issues are opened up for discussion and perhaps addressed in a proposed change in those regulations. Most recently -- usually we cannot talk about the issues that are addressed in a proposed reg until it becomes a proposed reg. The reason I can speak about this is because this regulation was discussed in a public meeting, the Task Force on AIDS Drug Development. Because that task force was particularly concerned about women who were excluded from certain studies of AIDS drugs because of a pregnancy or at least that there was a chilling effect such that investigators did not seek to involve pregnant women because of the additional paternal consent issue.

DR. CHILDRESS: Any comments you want to make on this topic? Others have suggested in passing in conversation today and other times the military, a concern that grows out of -- obviously out of the Advisory Committee on Radiation Experiments. Transnational research, which raises a lot of questions. And one could go on. There could be a long list. One could expand this list of subjects. Maybe for one reason or another they require some special attention.

Eric was concerned about how far this list might go, but one can point to certain kinds of features in either the individuals or their circumstances or their settings that might make at least attention to this from an ethical standpoint quite appropriate.

But any comments on that before we turn to IRB's?

DR. CASSELL: Well, I actually -- I mean, the list gets -- my concern, of course, is that you get so defeated you cannot get anything done. On the other hand, that is the generalization. I have a feeling that we could generalize better, abstract better and come up with things that

had to do with all of these groups that we clearly do not yet understand because we have been looking at them as separate groups.

DR. CHILDRESS: Arturo started out with his opening comment offering a definition and whether that would finally succeed or not. He was offering it really as a tentative way to think about this. That is certainly one way to go.

DR. BRITO: I think --

PROF. CHARO: Could you repeat the definition, Arturo?

DR. BRITO: Of vulnerability? Anyone that is set up for potential abuse by someone in a position of power, whether it be economical, educational, cognitive, physical, political or geographical.

DR. CASSELL: Anyone who would be at risk because of those things?

DR. BRITO: Yes. Basically anyone has the potential for being a victim. Anyone. Anyone in this world, right. But I think if we approach -- the way I am looking at this, if we approach anything that we -- any recommendations that we make from the point of view of the -- of any vulnerable group or a person that can be the most vulnerable, I do not think we can go wrong because that is going to apply to everyone else. Okay. So I think making general -- specific recommendations based on general assumptions.

DR. CASSELL: I mean, we -- in fact, there are the -- certainly the sick patient in a clinical trial is at risk because of a disproportionate power relationship with the investigator. And to be a concrete example of it, at Sloan Kettering what I suggested was that the clinical investigators had conflict of interest and they were not aware of it. They just were

outraged at the thought that they did not have their patient's best interest in mind. And I said, "Well, if you have your patient's best interest in mind before everything else you are doing a lousy job because you are supposed to be dedicated to obtaining knowledge from your patients and there is a conflict about that."

What is the solution to that? In that setting it was that there should be somebody whose primary responsibility was clinical care. I do not think that has quite happened yet. But, in fact, that does mitigate it. In children, also, if somebody's primary responsibility is the care of those children separate from the research effort it would solve it. If somebody's primary responsibility was the care of the pregnant woman apart from research being done it would help mitigate it.

The same thing is true of -- one of our guests pointed out to me that the cardiology consent form is six pages long. Then once again if somebody's primary commitment is to the care of those patients and they are separate from the research, a physician, then that helps solve that problem.

I personally am not troubled by the manpower implications of that. It is your job --

(Simultaneous discussion.)

DR. CASSELL: Private practice is getting to be --

(Simultaneous discussion.)

DR. CHILDRESS: We will take another comment or two on this question about vulnerability or there might be directions we could go perhaps building on the suggestions that have been made that would help us tie all this together.

PROF. CHARO: Yes. I am very supportive of doing something like this as opposed to talking about specific populations. I am not yet sure if we can do it. It might make sense to make homework assignments for ourselves to go ahead and try to write something up and see if we could do it.

I think, though, that another way to try to capture all that, and that might be easier for testing against our intuition, might be to think about what it is that renders vulnerability. Because, in fact, we usually say they are vulnerable with several different meanings in the reg.

I mean, pregnant women are not vulnerable in the sense that they cannot consent the way cognitively impaired and children cannot. They are, in fact, not vulnerable at all. It is the fetuses that are vulnerable because they are not on the radar screen of the regs. What was the view originally? Was it that the pregnant women are incapable of making decisions?

DR. LEVINSON: No, they still are under the possibility of coercion or requiring the cooperation of the doctor in a way that puts them in a situation of vulnerability.

DR. CASSELL: After they deliver a baby that is not the time to go sit down and have a big discussion about the rights or the wrongs or the ins and the outs.

PROF. CHARO: That would not be pregnant women, that would be women on the verge of delivery. When I am two weeks pregnant I am not vulnerable to the doctor and can say I do not want to be involved and I will go to another.

DR. LEVINSON: Yes, but --

DR. CHILDRESS: So, it is an area for special concern.

PROF. CHARO: Let's just say that I think that the situation of pregnant women is distinctly different from the situation of cognitively impaired people and children although we treat them all the same. But I think that if you were to think about populations that are vulnerable by what makes them vulnerable. I think the first one you would have to pick would be those who are totally uncovered by the regulations right now as the most vulnerable. There is nobody looking out for them at all, number one.

Second, would be the ones who are essentially uncovered because there is almost no implementation. Some of the worst scandals may very well have come out of intramural as opposed to extramural research to the extent that that is documentable. That may be the second most vulnerable population.

Then you get into the fact that actually -- kind of more concrete, the ones we are talking about, cognitively incapable of using things like informed consent for self protection. Basically cognitively incapable of self protection and/or subject to medication because they are hoping for a cure.

I can tell you right now that if you name any experimental drug that is designed to treat obesity I would sign up and I do not care what the risks are. I can only imagine that people with even worse problems have the same inclination. Those that were totally off the radar screen in terms of being considered, which I think would be the future generation problem. Those that are subjected because of institutionalization and by extension the military. And those that are

subjected to the patient because of economic stuff, which is very similar -- just trying to put examples to your thoughts.

But I really do think that it might be that this is going to be a very profitable way to go because it may be that you would be able to then say this person has seven vulnerability factors and now our presumption is we do not use them unless we have a strong justification.

DR. CASSELL: Yes, but then once again you get into -- now you get into the other problem. The problem is not merely to protect in some bland fashion that no injury come, it is to protect them in the sense of getting treatment for it, making sure treatments are available for their diseases. That is protection also.

(Simultaneous discussion.)

DR. CASSELL: So if you do it this kind of way, you are struck -- you need help the most and therefore you are out.

PROF. CHARO: No, no, no. I am only saying that potentially if you could list a fact -- list a bunch of things like he was trying to do, like I am trying to do that explain what it is that makes people less capable than the kind of idealized, fully well, fully financed, fully health insured, fully well connected to the medical establishment, a subject who has the fullest freedom to say no thanks.

(Simultaneous discussion.)

PROF. CHARO: Every factor that makes you less -- that have fewer degrees of freedom than that idealized subject would only generate then that much regard for the protocol and the extent to which it is going to be for your benefit and it is not -- it is justified on other grounds such as desperate scientific need or desperate, et cetera, whatever. It just creates

a kind of balancing process with presumption. That is all. I am not disagreeing with what you say is part of protection.

DR. CHILDRESS: One thinks about vulnerability and knowledge that -- not as a concept that brings out necessary and sufficient conditions, but rather as a family concept so you have got a lot of factors and --

PROF. CHARO: And I am happy to go with the word vulnerability because --

(Simultaneous discussion.)

PROF. CHARO: -- of the connotations associated with that.

DR. BRITO: Okay. Before we go away from that word I would like to give a concise definition of broad applicability of vulnerability.

Vulnerability is once again by definition -- what I have got right now is a lack of choice or a perception of lack of choice. It is a person that does not have choice or does not believe he or she has choice. That is vulnerability. Every one of these groups would fit into that criteria. Somebody who is cognitively impaired may be in a situation where they either do not believe they have a choice or they may not be given a choice. A child, the same thing. A pregnant woman may actually have a perception that she did not have a choice therefore she is vulnerable.

PROF. CHARO: About what?

DR. BRITO: About a decision for a HIV positive pregnant woman, does she have a choice of whether or not to take AZT during the pregnancy even though it has been proven to reduce the risk of transmission of the virus to her child?

PROF. CHARO: Well, she probably thinks she has a choice

but actually she does not have. Is that what you mean?

DR. BRITO: Right.

PROF. CHARO: But you are talking about the reverse where people do not think they have got a choice and they do.

(Simultaneous discussion.)

DR. CASSELL: Wait a minute. Does she have or doesn't she have?

PROF. CHARO: The law says she does but in actuality she would never get to the point where she could assert a legal right.

(Simultaneous discussion.)

DR. CHILDRESS: In other words, funds are not provided for every pregnant woman to get AZT. Okay. I think this is a --

(Simultaneous discussion.)

DR. CHILDRESS: -- direction. I think we also had an interesting exchange among subcommittee members.

DR. CASSELL: So can we -- let me go over the points --

DR. CHILDRESS: Okay. Last comment on that because I am conscious of our time.

DR. CASSELL: I can wait.

DR. CHILDRESS: Okay. But this is something --

(Simultaneous discussion.)

DR. CHILDRESS: This is something that we certainly need to do and I think we could do in interesting ways.

Okay. One of the big concerns in this whole area is a procedural one and that is how one is to understand and assess the role of IRB. Does anyone want to kick that off or shall I keep on? Anyone?

Well, the shifts that have occurred, and some of this we talked about earlier, have also had a major impact on IRB's. Shifts in terms of the increase in the work load. Shifts in terms of sources of funding that create conflicts of interest.

Shifts that are very -- make the research -- things that appeared in the Pennsylvania Center for Bioethics discussion shifts away from the model of research that was dominant in mid '70s where you had a research award given to a single investigator and a single institution for a small number of subjects. We know that contrast. We have already talked about it this morning in terms of a multicenter, multisite studies and the like.

But then there are also are problems because on the other hand -- I mean, if you look at the literature that is available on a couple of pieces I have put in the packet, you get two different perceptions that may not be totally unrelated. The column for IRB's, on one hand you get the sense that IRB's are being snowed under with bureaucratic requirements and problems in terms of bureaucratic stress, motivation people to serve, lack of adequate support from institutions, heavy work load and the like. That is one vision of the problem IRB's face.

The other vision, which appears in the Edgar Laughlin (?) discussion and to some extent in some comments from the IOM report that you had access to earlier, are problems of variability and lack of accountability. So you get two different directions in the assessment of what plaques IRB's at this point.

So we have to deal with that and try to sort out what is going on there and in that regard you had the GAO study circulated before

the first meeting. You also had an indication from Charles McKay that the study that he was working on would take place within a few months, but I understand and I am not sure -- that may not be the case, so I am not sure we are going to be able to draw on that. I understand it may actually be on hold at this point.

Anyone want to comment on that? He is not here. He is out of the country.

MR. DOMMEL: Yes, I think we know that it is going on but I think it is that the results may not be available before the -- I think it may be --

DR. _____: I think it is too optimistic to think you will have a report available in March. It is overly optimistic.

DR. CHILDRESS: Overly optimistic. Okay. So by August or any sense? At any rate it is not something we could perhaps have available to draw on. It would be important -- one of the things to keep in mind is what kind of information we need.

Then other kinds of issues that come up, one would be, for instance, the role of the DSMB, which in some ways, particularly for multicenter trials, does a lot more of the hard work, particularly in the ongoing monitoring of the trials than the IRB and often reporting information back to the IRB. So this is another level of ethical review that continues but does not always relate to what the IRB's are doing.

Then we have problems that arise because of special controversial cases. The most recent being a clean needle exchange program where an ad hoc committee was set up to evaluate that. What is the role for such committees? Should they play very minor ad hoc roles?

Should there be a kind of super committee to look at certain kinds of research?

I mean, perhaps we want to call on the earlier model of the Human Gene Therapy Subcommittee and the RAC for certain kinds of protocols, perhaps gene therapy, perhaps xenotransplantation. And we want to perhaps think of some that we might want to have a committee of this sort to deal with.

Or perhaps you want to go to regional kinds of committees. There are many different kinds of models and it is not clear that we want to in any way modify the current arrangement, but I would just note that certain kinds of modifications have occurred de facto with special ad hoc committees with something like the RAC for gene therapy experiments and with the Data Safety Monitoring Board playing a certain kind of role. So the system has evolved. It is not the same as it was in the mid 1970's. So we need to attend to those kinds of changes and then ask questions about whether further changes are needed.

I do not have -- I am not offering any recommendations for those changes, but those are at least some of the issues it seems to me we ought to be thinking about.

The big question to ask is whether we have or can we get in a reasonable period enough information to be able to make some kinds of judgments and that information really has to do to a great extent with the nature, structure and functioning of IRB's.

So I will just throw that out and see what kind of response you might have.

PROF. CHARO: Can you help with an ordering problem? I

have no -- I have no doubt that we can all detail some of the reasons why IRB's have this variability that we perceived anecdotally in their capabilities and in their effectiveness. We have heard hints this morning already about some of the new things that have developed making it ever more difficult in terms of multicenter studies, the phenomenon of private sector sponsored research which often just ups the overall work load in an absolute sense, and similar factors.

What would work with IRB's, and I am thinking now mostly in the extramural context, I am trying to keep straight the context in which we are working at each time, intramural, extramural, totally unregulated and uncovered. Part and parcel of figuring out how they work best is not only understanding the structural incentives they have got and the problems that they have got, but also what they are expected to be doing, which is tied so closely to the substantive discussion that we had this morning. I am feeling a little flummexed at how to approach this. I wonder if you could help kind of set up some --

DR. CHILDRESS: Well, I think that is something we are going to have to decide as a group where to go in first or go in simultaneously. So I mean I am not sure we have any particular way of doing it. I mean, I think one can distinguish but not separate the procedure on the substantive. I quite agree with you.

One way one could think about it is what some would call outcomes based evaluations of IRB's and we would have to think in terms of what they are doing, but that would be relative to the standards that we employ and what kind of decisions do we make, et cetera. So obviously the two would be closely connected. We would take that kind of approach

versus a much more strictly procedural one. So I, too, would see the two as --

PROF. CHARO: Right. So do you have a suggestion at exactly which corner we punch the hole?

DR. CHILDRESS: No. No, I do not. I think we -- the reason --

(Simultaneous discussion.)

DR. CHILDRESS: The reason I want to hold off on that is I think that we have to make a decision about that relative to the other matters in a few minutes. I think what you are talking about are things we can discuss before then. But I agree with you that that is going to be a difficult question. But here again it is one in part as to whether we get the information needed.

I mean, it is one thing to say that certain kinds of substantive standards are needed because we can see the kinds of problems even if the problems are few in number.

PROF. CHARO: Right.

DR. CHILDRESS: But then it is another thing to talk about the IRB's in terms of the system as a whole. I mean, if the variability occurs only in one or two outliers then that may not be too much of a problem and it may not -- the variability may be within an acceptable range anyhow. But how would you get that information is I think a difficult matter and best to open it up for broader discussion.

PROF. CHARO: Well, one question about information availability, though, outside the McKay thing. I guess OPRR is the right place to ask. To what extent can we have access to appropriately blinded,

coded summaries of investigations that might help us understand better how IRB's fail and understand what causes them to fail, and is there any place we can get any kind of examples of IRB's that have worked. Even though it will not be kind of statistically significant it would give us a much better understanding of all the details.

DR. ELLIS: We would be pleased to provide any reports of closed investigations and we have a fair number of those. We get requests from professors teaching ethics courses from time to time for the same material and they find it useful.

PROF. CHARO: And for those that worked is there anything that you can imagine pointing us to?

DR. ELLIS: Well, our office does not have routine documentation of IRB's that work.

PROF. CHARO: Okay.

DR. CHILDRESS: Other comments? I think this would be something worth pursuing, though, on the closed investigations. That could at least be useful.

PROF. CHARO: But one other piece of information that might be useful and might be accessible through things like the AAMC or some other type of medical school organization is in light of changing financing of medical schools -- of medical education. The degree to which there is an active effort to recruit privately sponsored research to be run by med school faculty and affiliates as a source of funding. It is something that has direct impact on both the kinds of the things that the IRB is reviewing and a number of things, and I sense that there is a potential trend there that we should not miss.

DR. LEVINSON: The trend is actually in the other direction. Industry is moving away from conducting clinical trials in academic health centers to a setting of conducting them in clinical research -- contract research organizations actually.

DR. CHILDRESS: Do you know much about those IRB's that are associated if there are --

DR. LEVINSON: Well, that brings up a point that sort of keeps coming up of what is the universal research that may not be covered or is conducted outside of the Common Rule that has been referred to. There actually may be less of that than we were discussing but a certain amount that could be gray or is conducted by institutions that are unused to or new at having an IRB because these CRO's are under fewer constraints than academic health centers where they are receiving government research money.

PROF. CHARO: CRO's?

DR. LEVINSON: It does not mean that they are not under FDA control.

PROF. CHARO: Right.

DR. LEVINSON: Which, Gary, you could fall in on this, but just because they are not getting government funding does not mean that they are not required to have IRB's or to have informed consent. If they are doing the research in order to obtain FDA approval they have to follow FDA's regulations which are to a great extent consistent with the IRB. So it is not that it is totally unregulated by any means.

DR. CHILDRESS: The last time at the NBAC meeting -- the first we had where Gary made a powerful argument for an extension of the

Common Rule. Do you want to make any comment in relation to Rachel's point here?

DR. ELLIS: Well --

DR. CHILDRESS: About the extent of --

DR. ELLIS: -- as I said in October I would describe three domains of regulation. The Common Rule, which is research conducted or supported by the 17 federal agencies. There are other federal agencies that do not adhere to the Common Rule formally. There is an umbrella of protection conferred by FDA regulation. Then there is a third domain of research that falls outside of those umbrellas of protection.

DR. CHILDRESS: And one question is how large a domain are we talking about in that third category?

DR. ELLIS: I do not know how large a domain we are talking about in the first two categories. So, necessarily I do not have the third category.

(Simultaneous discussion.)

PROF. CHARO: This is really interesting. I see it from the med school institution side where the effort has been to up the number of pharmaceutical company sponsored trials enormously. You tell me that actually the trend is the other way and --

DR. LEVINSON: They are not inconsistent.

PROF. CHARO: They are not inconsistent. I know this.

DR. LEVINSON: Yes.

PROF. CHARO: But it reminds me of those things. But how is it that you are able to know that? I mean, what documentation is there out there of the amount of research going on, by whom, and where it is

being done? That is the kind of thing we have been asking over and over. Where is that? Where is it that underlies your ability to understand the trends?

DR. LEVINSON: Well, there are people here from industry that could speak to the desirability of moving -- maybe not desirability, but simply the facts, are they seeking other organizations. What I am hearing from the perspective of the academic health centers is that for one reason is because they charge 20 to 30 percent higher than a community hospital for care of the same patients. It is a cost issue. They are more expensive. You go to your community hospital first.

The CRO's are coming up because they are in existence solely to provide a facility for doing clinical research. They, therefore, are very efficient at providing that and providing the kinds of data collection, for example, that would be required to submit to FDA for an IND and a community hospital might not be as good at that. They have staff that are devoted to that as their only aim.

But I am hearing it from the perspective of academic health centers that are trying to become more competitive as you said just to get that money, but are finding that they are slipping. They are slipping in many ways. They are slipping in terms of not getting government funding either. They are not getting as much government funding. So, of course, they want to go wherever they can to get patients and to get revenues.

PROF. CHARO: So we understand from self-reports from industry what it is that they are trying to do now and planning for in the future, but we have not been able to confirm it yet in terms of knowing exactly how much is going on where.

DR. LEVINSON: Well, ideally FDA knows who submits, you know, all their --

PROF. CHARO: In the drug context, yes.

DR. LEVINSON: That is right as far as drugs are concerned.

DR. CHILDRESS: So do you think -- I mean, could we get some sense of the trends from the FDA then?

DR. LEVINSON: You have to ask them.

DR. NORTON: There are two potential sources of information --

REPORTER: Could you stand and come to the table?

DR. NORTON: I am sorry. Amanda Norton from FDA. It seems to me there are two potential sources of information. One, there is an industry group in Washington called Pharma that will probably be able to provide you with some kind of information on the research effort and the biologics component of that is called BIA. They probably have comparable information.

In terms of what information would be available from FDA about what kinds of organizations are doing the underlying research, I can certainly take that question back, but I will be very surprised if we could sort our data according to where the research is being done. I mean, we might know on an ad hoc basis.

Lee, do you have any idea?

So, well, it is probable that we would not be a primary source for the kind of trend that you are talking about, but I can certainly go back and ask the people who are in charge of that and who review our

IRB things, whether or not we have anything that would be useful.

DR. CHILDRESS: If you would, that would be helpful. Thanks.

DR. TITUS: Sandy Titus with FDA also.

REPORTER: Would you please stand and come to the table? I cannot hear you. You have to stand in front of the thing.

DR. TITUS: I am on the Human Subjects Protection Team at the FDA and I cannot give you any definitive numbers but I have a sense like you do of a trend of CRO's doing more work in the field and actually setting up IRB's because I have reviewed some of the IRB's and it is very disconcerting because of what I see as an inherent conflict of interest but we have no regulatory ability to comment on them in any way, shape or form. But they are getting the contracts. They are setting up their own approval system. But we have no numbers on that within our office except to say it is happening.

DR. CHILDRESS: Okay. If you think of any way we could get at that information if you would let us know.

DR. CASSELL: Just as a point of information, they could be legislated under control. Legislation could be written that would bring it under control. Is that correct?

MR. DOMMEL: Yes.

DR. CHILDRESS: So is the implication of that don't even bother to find out, just legislate and that will take care of the problem?

DR. CASSELL: No, that is not the implication. The implication is just what it sounded like. I mean, I hear that it is an increasing number and know that that must be true because I know it is

happening in my medical school. So I mean I do not know whether -- I ask only to carry the question further, is there large resistance against that? It is not the first time the question has ever come up I am sure. So is there resistance in the Congress about legislating things like that? Is it an issue? Does anybody talk about it?

DR. LEVINSON: I would -- I think the chances of legislation would not be huge.

DR. CASSELL: That is what I want to hear. I mean, I did not want to hear that particular answer.

(Simultaneous discussion.)

DR. CHILDRESS: Okay.

PROF. CHARO: Once we are able to really sit down and make a matrix of who is a subject and where, and what protection if any applies to them, it will probably be a good moment to sit down and figure out for each one of them what it would take to bring them under some protection and if it is politically feasible at either the federal or the state level, and by administrative regulation or by --

(Simultaneous discussion.)

MS. FLYNN: It is a particular -- I mean, we see a lot of this moving to CRO's with psychiatric research. We have a vulnerable population and it is not enormously well protected in the current setting now moving increasingly in disease settings where they are creating their own IRB's and appear to be sort of outside the general purview of much of the responsible research establishment. It is an issue and it is a big trend. It is a very big trend.

DR. MANGEL: When the Common Rule was being

considered and even when its predecessor was being considered one thing that was argued about was whether to try to extend it not to all research but to extend it at least to research that was being done in facilities that were funded by the federal government, that is not only the research itself that was funded but all your research, and trying to reach the institutions in a constitutional way by saying, well, if you take our money here is what you have to agree to.

In both cases the department and then the agencies together in adopting the Common Rule chose not to do that. I guess the thinking being that they are biting off enough and that they ought to shoot at a more limited goal. Then there were also ideas of the federal government fooling around in the business of nongovernmental agencies. But there was this debate and the opt thing was on the side of the more limited approach.

PROF. CHARO: But it is worth noting that states do not have nearly the same issues about their authority. They can regulate any business in their state and --

DR. MANGEL: That is correct.

PROF. CHARO: -- obviously there are interest groups that will line up for and against. From a political point of view it is hard to argue publicly in an advertisement against the notion of having people protected from research abuse. So it is a very difficult kind of debate to anticipate and see how it would be played out. I am just trying to say that there are many different angles from which you could tackle these things depending on how important you thought it was to tackle.

DR. CASSELL: Fifty different sets of regulations.

DR. CHILDRESS: An uncommon rule there.

DR. EVO: I am Grace Evo with Eli Lily and I just want to comment on CRO's. If a company makes a decision to use a CRO generally the company is going to evaluate that CRO to make sure that the data that is derived from that work is going to be usable for a drug submission. So the worse thing that could happen would be for a company to pay serious money to a CRO and have the data thrown out because an IRB was not properly constituted or some other mistake.

Generally CRO's with their own private facilities are in Phase I or Phase II levels of research. They are in the early stages. But if you go into a major trial in a Phase III where you are talking about thousands of patients you are usually back at a hospital setting or a university setting with an independent IRB associated with that institution.

So it is very rare that you get to "the pivotal" studies for a drug submission within little CRO's, Phase I or Phase II clinic. That would not happen. Almost all pivotal studies are investigated by FDA and they are very closely monitored for human subject protection at that stage.

So it would be earlier in the research that a CRO dominated type scenario would exist, but even then they have to be reviewed for the appropriate Part 50 of the regulations or else the data is no good to the company.

DR. CASSELL: Well, it makes clear once again that it is a whole area that we do not know anything about. How many people we are talking about.

DR. CHILDRESS: That is right.

DR. CASSELL: How many IRBs are we talking about and so

forth. The issue is how to find that out. That is not easy.

DR. CHILDRESS: But it is clear it is a very different world than when the Belmont Report principles were applied to it.

DR. CASSELL: Yes.

DR. CHILDRESS: And now we need to at least think about that work. Okay. Anything else about IRB's?

DR. CASSELL: How fast do you move?

DR. CHILDRESS: Pretty fast. So that we will --

DR. CASSELL: Well, I mean there is the issue in IRB's of inadequate training or a lack of expertise that we have not addressed, and that is a real problem. In my own experience with the IRB it took even people who were knowledgeable about the medical or the scientific aspects of it a year or a year-and-a-half to get up to understand what their role was on these committees and that this was not the enemy.

The whole bunch of things that happen when people first come on a committee and have preconceptions that have to be -- that they have to check against what is going on. Whether there is, in fact, any way of avoiding that. Is there any way of making an IRB more effective? Would changing the regulations having to do with minimal risk research really make a big difference? I think it would.

I think there is a lot of stuff that the IRB -- I submitted something which everybody accepted as trivial and had to go to two meetings and come back out. Somebody had to take a lot of time to do that and I think that is quite common. And whether, in fact, we could unload part of the burden of IRB's and that is in part a trade to negotiate what we are taking away from what we want to happen.

DR. CHILDRESS: And I think while you were out a larger version of this came up for comment that Alta made about the connection between the substantive standards of the criteria guidelines and the procedural interest from the IRB. This is one area where you certainly get the overlap relative to these standards. This could well have an impact on the functioning of the IRB.

Any other comments about IRB?

Two other points before we move to -- at least I can think of and you may think of others before we move to consideration of priorities. One we have just addressed briefly in passing and that is the question of the extension of the Common Rule, referring in particular to the comments that Gary Ellis and others made at the first meeting. And your comment that this may be the most vulnerable population of all and unprotected in that sense.

Anything else you want to say about the extension of the Common Rule which is certainly one of the topics that we need to address?

The last one I can think of and then -- quickly run through your mind others that we may not have brought to attention today, and that is the compensation for research related injuries which has been at least for the last 20 years a topic of discussion every now and then by this special committee or that special committee. The Secretary's task force that I think you were involved in, in the late 1970's, Bill, is that right?

MR. DOMMEL: Early '70s.

DR. CHILDRESS: Early '70s. Arguing for providing compensation for research related injuries. I will just use that broad category, but obviously we need to distinguish medical compensation as

covering medical problems from compensation for disability from compensation for death. There can be many different kinds of compensation. Compensation for lost wages as a result of a temporary disability, et cetera.

And then the President's Commission called for a small experiment after addressing the issue of a variety of standpoints. Then I think an ad hoc committee was supposedly set up to respond and so forth. I do not know what all happened after that. I think that the meeting --

MR. DOMMEL: Not much.

DR. CHILDRESS: Not much. Then at the meeting in San Francisco when we were talking with the international group obviously the medical coverage is not a problem in settings where there is a provision of universal access to health care. So it is a different kind of issue in that setting than it is in our own.

So we may have to address it apart from the provision of universal access to health care as a special column for those who have participated in research and have been injured in a context that falls outside the system so that victims of negligence or failure to get informed consent or something untoward happened to them in the process that could have been prevented. Then there are various kinds of arguments that dealt with -- by the HEW Secretary's task force that dealt with the President's Commission and so forth.

One big problem here is that at least at different times, and I think it is still the case, we just do not know all -- we do not have a good grasp on all the injuries that take place in a setting despite the adverse reports, at least with drugs and so forth. Is that still the case? Can we say

that? Or do we have a good picture of the universe of injury so that we would have some idea as to what we are talking about here?

Gary, I will turn to you with that kind of question.

DR. ELLIS: I get all the questions where there are no data.

(Laughter.)

DR. CASSELL: It is you that does not have the data.

(Laughter.)

PROF. CHARO: He is asking us to give him the authority to collect it.

(Laughter and simultaneous discussion.)

DR. ELLIS: You mentioned a small experiment that the President's Commission called for. I think the President's Commission also recommended the University of Washington, Seattle, as a self-insuring institution with respect to research injuries. And so there is no University of Washington here, but I believe that they could demonstrate a 10 or 12 year history now of handling their own research related injuries. The University of Washington is a major medical center with a major research portfolio.

So my best advice to the commission would be to call for testimony from UW and they can tell you about the incidence of research related injuries, how much it costs and how they handled the compensation. To my knowledge it is a self-insuring program. That is my best advice.

DR. CHILDRESS: Good. Okay. Thanks. Any other comments either about the possibility of additional information or other issues surrounding this topic before we see if there are other topics we

want to make sure we talk about?

PROF. CHARO: Yes. Just as a subset that it is not going to be any easier to take data in this area, there is no evidence that I know of that there have been large number of cases brought in reaction to injuries during participation as a research subject. To the extent that any cases have been brought, have gone to trial and have resulted in a verdict there is something called the Verdict's File so that that much could be gotten.

But for information on the number of cases brought and then the number of cases settled or simply dropped at the plaintiff's behest it would be an entirely different kind of research endeavor. I know how you can do it and I know the kind of people who could do it because they did it on punitive damages and exploded a lot of myths about the prevalence of punitive damages.

That is why I was querying where the info was coming from. I see now two very big areas of law where -- say people absolutely knew for sure had no bearing on reality and perception. So we have to decide whether that is worth trying to pursue. I suspect it probably is not because of the small numbers.

DR. CHILDRESS: Other points on this?

DR. CASSELL: Well, maybe, Alta, because when you know somebody -- you know how to get this information. It is expensive? Is it time consuming --

PROF. CHARO: Both. Because what you have to do -- this is what we found, for example, in the area of punitive damages. We were looking to see the effect of the threat of punitive damages on the settlement process because they wanted to understand not only when they

are awarded but how is it they influence people in bartering. What they had to do was first go through all the verdicts that had punitive damages. They contacted all the lawyers who had handled cases that involved punitive damages and said --

DR. CASSELL: I gotcha.

PROF. CHARO: -- what other cases have you done, what other people do you know, and it was one of these endless series of networking things until through the trick of some mathematician they got to a confidence level on how to cover the universe and that they felt like they had a database that they could work with. It was nightmarish.

DR. CHILDRESS: Other thoughts? Other topics that were not mentioned that ought to be part of our thinking as we turn in just a few minutes to trying to sort all of this out in terms of what we ought to do first.

DR. LEVINSON: We discussed education in several context but still not by itself. One of the group of recommendations that came out of the Advisory Committee on Human Radiation Experiments that dealt specifically with current research had to do with the centrality of ethics in the education of investigators, also talking about public discussion.

They have requested that -- they did not ask NBAC to look at this because they did not put in an exclusive recommendation that an NBAC like organization be established, although they came close to it. But the two -- two of their recommendations that deal with issues that you brought up today had to do with education and the centrality of ethics, and the other had to do more specifically with IRB's, which you have discussed today.

But there will be an interagency report coming out that

responds to the recommendations from the Advisory Committee on Human Radiation Experiments. Without jumping the gun on what they are going to say I would guess that at least in the recommendations having to do with current research centrality and IRB functions will be items that could be eventually referred to NBAC. So you might want to think about that.

DR. CHILDRESS: Thank you. Okay. Anything further you want to say about the education side of this?

DR. BRITO: Yes. It is just interesting that in the State of Florida and many states in order to keep your license as a physician, as a clinician, is you have to get CME credits in HIV disease and domestic violence every other year. I do not know how difficult it would be to recommend legislation to different states or to all states really requiring CME credits for any principal investigators, et cetera, in order -- I do not know. But that point is well taken with the education. There is no requirement right now as far as I know in any state for any principal investigators to have --

DR. CASSELL: Well, I am sort of wondering whether to discuss it now or wait until we get to future business because I want to pick up on education. I think it came up a lot in our discussion and now you tell us it has come up also in the radiation issue. So you are in the chair, when do we do it?

DR. CHILDRESS: Actually a little bit now would be fine. What we are going to do in the next part is actually decide what we are going to do first and when and sort of structure --

(Simultaneous discussion.)

DR. CHILDRESS: So say more about it now as an

independent topic.

DR. CASSELL: Most medical students now by the time they graduate have had some training in ethics. Many medical schools now have courses in ethics. Maybe all of them do. I do not know. So that the group of investigators who are recently out of medical school have more exposure than the generation before them. But it is not specialized and it is not -- well, it is not specialized. It is not directed --

PROF. CHARO: Substantial.

DR. BRITO: It is not emphasized.

DR. CASSELL: It has not got to do specifically with their line of work which is working with human subjects. There are issues of research ethics that do not have to do with human subjects which could well be emphasized. But my own sense of it is that it ought to be substantial training during the investigator's career. This is a part of investigative research just as other methodologies are and just as statistics are. They will probably treat it with the same joy that they treat statistics, but nonetheless they all know that is essential now and they did not 20 years ago.

So my feeling is that as a substantial recommendation that training about ethics be part of an investigator's career. Not some add on thing that is two hours once a year which is the way it is now, whatever, which is close to that. That would be a major thing we could do. There are people to teach it now. I mean, it is a whole different thing than it was a while back.

MS. FLYNN: I would endorse that and again just coming from the experience of having seen some of this, the problems that have

emerged in recent years in research with psychiatric patients and the relatively weak response that the profession has had, the medical profession, to deal with and perform this research in terms of oh, my gosh, we better get out there and get some training together. It has been relatively little even in the face of some significant problems that have been brought forward by the profession.

OPRR has done some things. There have been some movement. But I think there is a signal that needs to be sent, that needs to be strongly sent.

PROF. CHARO: Eric, you said something about it being a requirement that investigators get two hours a year?

DR. CASSELL: Well, maybe not two, but it is close to two. Whatever it is, it is a lecture and a seminar at Cornell. And our's is similar to the Rockefeller, Sloan Kettering. At Cornell I participate in it once a year and it is minimal. It is a joke.

PROF. CHARO: Required by whom?

DR. CASSELL: I think it is --

(Simultaneous discussion.)

DR. CHILDRESS: We have it at UVA too. So how does one state the requirement?

DR. RACHLIN: I am Joan Rachlin and I work with --

REPORTER: Could you stand please?

DR. RACHLIN: Certainly, sorry. The NIH, Office of Extramural Research, promulgated three years ago a regulation that all -- initially it applied to all T31 and T32 Chinese that they undergo something like two to three hours a year of education in the responsible conduct of

research. And various medical schools and educational institutions have translated this differently and it has mostly inched along being as individual as the individual institutions themselves.

This past year the Ryan Commission reexamined that requirement in the broader context of some both recent cases that have arisen, but mostly in the context of the changing and rapidly changing context of health care research, and decided that that requirement should be extended to all researchers, to all those involved in research enterprise both private and not for profit. There has been a great hue and cry from the research community and so far there has been no resolution as to whether in fact the requirement will be extended to researchers as opposed to just the trainees.

At the institutions which have taken it seriously they make a very strong pitch and involve faculty at the highest reaches so that other faculty and other researchers come. Certainly the requirement is not that every faculty would have to sit in an audience. Some would be involved in developing materials, others would be involved as teachers and lecturers, et cetera.

But clearly the sense of the Ryan Commission was that the future of the scientific enterprise is currently under challenge if not frankly imperiled and that really strong and serious and consistent education was the strongest key to reversal or at least a slowing of that process. There is now movement in certain quarters to try to give some teeth and life to this commission's recommendation.

DR. CASSELL: In our institution the majority of the attention is not given to human subjects, it is given to the --

(Simultaneous discussion.)

DR. RACHLIN: It is true, it is quite possibly in a context of research.

PROF. CHARO: Right. So it is a scientific problem. Integrity is what I had always associated with it, but we have a small research ethics with human subjects component.

DR. RACHLIN: Yes. Some of them include human subjects, animal subjects, clinical research. I mean, again institutions have interpreted it and thus implemented it quite differently.

PROF. CHARO: And in what basis would there be authority under whose jurisdiction to impose this requirement on all researchers in the private, not for profit -- the for profit and not for profit, the public sector?

DR. RACHLIN: Again it was a recommendation of the Ryan Commission on research integrity.

PROF. CHARO: Okay.

DR. RACHLIN: It certainly has no authority at present. It was a recommendation strictly voluntary. But there have been many voluntary and professional organizations such as, for example, the Institute of Medicine that have begin to endorse this on limited levels recognizing the obvious both financial and other logistics, or the patients. But I think a lot of people feel that the time has come and it has got neon lights flashing wildly. Education is the greatest deficit and cause of the problem and thus needs where the energy and money is spent.

PROF. CHARO: Sure.

DR. CHILDRESS: What is your sense of endorsement in the

private sector?

DR. RACHLIN: I do not want to be too cynical but in fact it seems as though -- again this is all quite new. But in general it seems as though there is lip service and some head nodding and communal hand wringing, but there does not seem to be any widespread support. I think credibility at the highest reaches is going to have to come from the federal government and from again AAMC and the Institute of Medicine. I think it will have to come from those places and then industry will follow along but will not lead.

DR. CASSELL: And our -- originally I understood it, but when I was talking was that the research establishment -- this is not a way of saying you have to teach your subjects better. It is understand that this is a collaborative effort. Your subject and you are part of a collaborative effort. It is a change in your understanding of your relationship to subject just as in the practice in medicine there has been a change in understanding of the relationship of doctor and patient in this last generation. It is that same kind of thing.

MS. FLYNN: But that is not what she said.

DR. CASSELL: No. That is not what she said.

MS. FLYNN: I think that is an important thing to say but that is not what she said.

PROF. CHARO: But it does raise one last thing actually and maybe it is worth putting on the list as we then move into priorities. That is from a researcher's point of view what are the frustrations and obstacles because with such a strong focus so far on subject point of view, which per se I endorse, the risk is that the result will be a collection of

recommendations that would so frustrate the research community that you would once again be in a situation where people are looking for ways around regulations that they think would be trivial or unnecessary, irrelevant in this case, et cetera. So a better understanding of where they see obstacles, which is what you had alluded to very early on, might make for a better sense of how --

DR. CHILDRESS: We saw a bit in the IRB as one part of this picture.

PROF. CHARO: Yes.

DR. CASSELL: It is not clear to me. I mean, when you start to educate people -- unless you are doing this kind of education which is not really education, this is resuscitation training. Every year you have to take the resuscitation training lest one of your colleagues dies at your feet.

But this is -- we are not talking about the same kind of thing. We are talking about changing the educational priority within the research establishment and that is not going to happen because somebody -- that does have to happen because it comes from the AAMC or the IOM and the government. That is where it has to take place.

DR. CHILDRESS: This is probably something that Diane Scott-Jones would have raised had she been able to be here at the meeting. She raised it in San Francisco as part of our international gathering. That is issues of cross cultural sensitivity. Now we are raising it in terms of the transnational context of research. But much broader than that, it seems to me that is an important part of the picture for the educational process. But we will get to hear more from her at the next meeting.

Unless there is some other topic we ought to add let's spend

the next 45 minutes trying to decide what we are going to do when.

DR. CASSELL: We had one more comment.

DR. CHILDRESS: I am sorry.

DR. RACHLIN: I just wanted to comment on, I think it was Alta's question about -- or perhaps Dr. Cassell's about what the research -- what the PI's frustrations were and we have just completed a very small and certainly not scientific, a small study of how IRB's and health services researchers feel about the problems that plague each camp because there have been a lot of concerns and, in fact, a lot of complaints that IRB's do not understand health services research and vice versa. So we have done a small study on that.

To the extent that the data is generalizable, I do not think it would surprise anyone to know that PI's feel that IRB's are perhaps obstructive, a lot of red tape, delays, delays, delays. You know, again that they really have a basic misunderstanding of both the nature of what they are trying to do and the importance of what they are trying to do.

When we presented this at primer meetings people have just rallied and said it is not just health services researchers that feel this way about IRB's, in fact it is researchers in general in many quarters. Again not trying to generalize unreasonably. But when you ask what are the PI's concerns and complaints I think those are the nub of them. Similarly IRB's feel that it is the converse set of complaints.

DR. CHILDRESS: Could you make a copy of this available? Is there a --

DR. RACHLIN: I am just finishing up a summary and I would be happy to --

DR. CHILDRESS: Okay. If you would that would be great.

DR. RACHLIN: We did it pursuant to a grant from the John Hartford Foundation.

DR. CHILDRESS: Okay. Thanks very much. Okay.

Colleagues, do we do all of the above? What do we do first? What are your wishes in terms of what is ideal and what is feasible?

DR. CASSELL: Why don't you give us a summary of what is in front of us?

(Simultaneous discussion.)

DR. CASSELL: What are you asking us to do?

DR. CHILDRESS: Well, then what I would recommend you do is to take the agenda for today and just glance down at it noting that IRB's should be added to the list and education should be added to the list, and then there will be several subsets of each of those. This would probably be the best overview of what we have covered today.

What we have to think about is what we are going to recommend or what we are going to present to NBAC in just a few weeks as a proposed work plan and in that context a rationale for why we think that work plan is appropriate.

DR. CASSELL: Well, I think that we would make a major contribution if we could cut the knot that troubles everybody about vulnerable subjects. I think Arturo's suggestion is a very good start. For one thing in clarifying the vulnerable subject we clarify all subjects. That is actually what he did. In essence, he says, "All subjects are vulnerable." But as it says in -- some subjects are more vulnerable than other subjects. 1984. Some subjects are --

PROF. CHARO: I think it was Animal Farm.

DR. CASSELL: Yes. That is right. Some subjects are more vulnerable than other subjects. But the basic understanding of what makes somebody vulnerable is there. That does not address the issue of can you give consent for another person to be put at risk, but it does raise that issue. And then that would bring us into the problem of informed consent itself. And they would feed each other rather than getting us going off in two different directions.

MS. FLYNN: I really want to endorse that. I think that these subjects need to be considered together. I think that Arturo has given us a very good way to look at some of this and I would see that as very helpful. It is a very helpful approach.

DR. CHILDRESS: I think another way in which it is helpful actually is to go back to the changing paradigms because by focusing on vulnerability the way we have is a way to deal with both the problem of --

(Simultaneous discussion.)

DR. CASSELL: Yes.

MS. FLYNN: Right.

DR. CHILDRESS: -- need protection as well as the need for that conclusion. So it is a way -- it could be potentially a very useful way of illuminating the area and at least casting --

(Simultaneous discussion.)

DR. CASSELL: And it might also help us focus the educational issue rather than getting stuck in you must have respect for human subjects, watch out for kids and pregnant ladies, and other rather crude ways of doing it.

PROF. CHARO: Can we somehow capture in there -- the definition that we are focusing on is the one that has to deal with constraint on choice. Is that the one that you had in mind or the one that had to do with power?

(Simultaneous discussion.)

DR. CASSELL: Primarily power.

DR. BRITO: Choice, except for pregnant woman and --

PROF. CHARO: Right. Yes. I always get sticky on that stuff. Can we capture in this somehow the consideration of people who are not covered at all and then we will focus later on how many of them we guesstimate there might be and in what settings, and how vulnerable they are exactly, but to make sure that they do not drop out of the radar somehow? I do not know that they fit into a definition, but somehow --

(Simultaneous discussion.)

PROF. CHARO: People who are not covered by any set of protections because it is not a drug, device or biologic study under FDA. It is not federally funded and it is not taking place at a site that is subject to a multiple assurance that requires compliance with the federal rules. So, therefore, they are in a totally unregulated, unmonitored setting.

DR. BRITO: Is that not in the exclusion criteria? Maybe I do not understand what you are -- see, I am taking that to include -- when we say exclusion --

PROF. CHARO: Okay. Fine.

(Simultaneous discussion.)

PROF. CHARO: So it is going to be the access to the research as well as access to protection from the research?

DR. BRITO: Yes.

PROF. CHARO: Okay. That is fine. I just wanted to make sure that it did not get dropped.

DR. CASSELL: We are talking about -- in other words, we are talking about what is our relationship to the subject. What do we owe the subject and that is what could make them vulnerable.

PROF. CHARO: Right.

DR. CASSELL: And how do we assure that whatever we do owe the subject we are actually meeting in terms of getting consent and so forth.

DR. CHILDRESS: I very much like this direction. I think it could be again very useful as a way to start. Let me just raise what I could imagine being --

DR. CASSELL: Mm-hum.

DR. CHILDRESS: We have been through now a long period in which we really have been interested in doing is empowering people by recognizing them as agents to make their own choices and so forth. To focus on their vulnerabilities is now to focus on the other side of that. Part of our task I think will be to get these things together and that is why the choice part that you mentioned there in the other definition is important. I guess in setting it up this way we are going to have to be able to include the other very effectively or else this will be only a partial picture.

DR. CASSELL: But that is one of the interesting things about the whole business of people adding agency -- rah rah agency that it has -- it has been blind to the vulnerability that goes with agency. So to have agency is to be invulnerable and it is not that at all. What we are

trying to do is give people agency at the same time as they are protected so that they can exercise their agency.

DR. CHILDRESS: Right. Again I think it is -- I think you are right. I am in accord with it. I am raising what I think will be one of the first objections to come up and we need to attend to do it. Now of course we are still at the preliminary stage in developing it and there may be unique ways we can accommodate that anyhow.

DR. CASSELL: Yes.

DR. BRITO: To add to that, when we tie in the vulnerability to the informed consent issue, I think that is where I would make another point about making informed consent not such a passive process but more of an active or collaborative process between the investigator and the research subject. I think that will entail more of the empowerment issue and make someone less vulnerable.

MS. FLYNN: This also allows us to bring back in some of the issues around the community of interested participants in creative ways to help support.

DR. CASSELL: Given some luck in working it out, I mean because it will take -- it will take --

(Simultaneous discussion.)

DR. CASSELL: Given some luck in working it out then we do meet with our desire to move ahead rather than just, you know --

MS. FLYNN: Right.

DR. CHILDRESS: Yes. And I think this -- it seems to myself it would actually be an exciting way to go about it.

DR. CASSELL: Yes.

DR. CHILDRESS: It is not simply tinkering with what is there, but actually trying to capture something that in addition that could be powerful for educational and other purposes.

PROF. CHARO: So one ball of wax essentially is going to be kind of the substantive goal where you are talking about what subjects are entitled to and what prevents them from getting it, which in part is going to be related to the objectives of research and the structural incentive that drive researchers, institutions, et cetera.

DR. CHILDRESS: Those changes, right.

PROF. CHARO: And all those changes and how that results in certain kinds of vulnerabilities and certain kinds of special attention deserving situations. And I suspect, although I do not know how to -- it is hard to do it in a setting like this, you could probably go through that and then identify the key data areas where in order to do that well --

DR. CHILDRESS: Okay. What we need --

PROF. CHARO: -- we need to know more and we need to be able to remind ourselves of what we can find out and what we cannot find out at all.

DR. CHILDRESS: Right. Some of the things I have flagged but I am not sure I flagged everything. We were asking about what do we need to know on the empirical side about the process of informed consent. Earlier than that, attitudes of subjects participating in research, why they accept or why they refuse, and what the experience has been. What is happening in IRB's across the board. Questions about the research setting. Those are at least four that I flagged and I may be missing something there.

PROF. CHARO: It may be possible to --

DR. CASSELL: We wanted to know what has taken place outside the Common Rule and outside the FDA.

DR. CHILDRESS: Right.

PROF. CHARO: As well as what is going on inside the Common Rule.

(Simultaneous discussion.)

DR. CHILDRESS: Right.

DR. CASSELL: Gary has got that at his fingertips actually. He just has not drawn it together. That is all.

DR. CHILDRESS: Is there anything else you can think of on the information side?

PROF. CHARO: Yes. I wonder, would it be valuable to get some serious briefing either orally or in documentation about the model that is used for animal protection because I have heard several references to why it is superior to human protection in some ways. It is a system that is in place. We have a history. We know how it works and we know how people have reacted to it and it may just offer some possible --

DR. CASSELL: Yes. You know what makes it work so much better? It lacks subjectivity. Animals do not speak for themselves.

PROF. CHARO: Well, they do. The question is whether or not we listen to them.

(Laughter and simultaneous discussion.)

PROF. CHARO: No, but there are other regards in which certain things like the data collection about the number of sites, and the number of animals, and the experiences, and the training, et cetera, are

substantially different and potentially than in the human area. And at least then if we are going to be focusing on what might be necessary to implement any new vision. It would be nice to know what has already been implemented and how strenuously people have objected to it. If they have not found it to be too much of a problem then it is a promising avenue.

DR. BRITO: I would go further than that. Not just animal studies but at the international conference -- we were just talking about this, Laurie and I, before the meeting restarted. At the international conference we heard some wonderful reports from other countries. We get locked into the sense that the U.S. does everything and we should set it up, you know, correctly, et cetera, et cetera.

But if we look at the Canadian system where they seemed -- I do not know because I do not know the data on that -- they seemed to have less problems with their research possibly because they have a more socialized system of medicine than we do and therefore less discrepancy between health care coverage. Therefore, maybe we want to look at those as models too and look at some information.

DR. CHILDRESS: And did everyone, including people who were not at the meeting, get the pack of materials?

PROF. CHARO: No.

MS. FLYNN: No.

DR. CHILDRESS: This is a huge pack of materials.

DR. CASSELL: Undoubtedly you will.

(Simultaneous discussion.)

DR. CHILDRESS: And should. Actually could we get that sent out, the San Francisco packet, for subcommittee members because

there really was a lot of very good stuff, particularly on the research side I thought.

PROF. CHARO: And the genetics materials so that we can --

DR. CHILDRESS: The genetics materials would be part of that. Oh, you mean from the --

PROF. CHARO: Yes. I mean --

DR. CHILDRESS: Yes.

PROF. CHARO: -- these things are going to be overlapping at a certain point.

DR. CHILDRESS: Right.

MR. DOMMEL: Where do we stand on the information from the San Francisco session of the commission? Are books available to those who were not there? Did we not prepare books for those who were not there or prepare a sufficient number for those who were not there?

DR. HULL: We have about three or four more.

DR. CHILDRESS: That may --

MR. DOMMEL: That may do it.

DR. CHILDRESS: You have one.

MS. FLYNN: I need one.

DR. CHILDRESS: Okay.

DR. CASSELL: No, I had mine. Thank you. I do not need a second one.

(Simultaneous discussion.)

MR. DOMMEL: Diane Scott-Jones was there so she --

DR. CHILDRESS: Right. So three.

MR. DOMMEL: Rhetaugh Dumas would need one.

DR. CHILDRESS: Okay.

PROF. CHARO: But it seems like because of the -- you know, realistically anything that smacks of changing the existing structure needs strong justification because you know that you have to sell it. Right? Somewhere along the line we have got to be able to test these ideals or test this kind of formulation against what has been achieved and what we think are the obstacles to further achieve them under the existing system and see whether or not it is, indeed, in need of real change or from a system's point of view you could tinker. I do not -- I do not feel like I know that yet. I know why the IRB's are struggling but I do not yet whether there is anything that would be so much better that would be worth the fight to try to achieve it.

DR. CHILDRESS: Right. Well, in some ways reformulating the basic paradigm and the kinds of principles at work in this way could lead to change in certain areas but affirmation of other areas. It need not be a totally revolutionary --

(Simultaneous discussion.)

DR. CHILDRESS: But we need -- in fact, this is just a suggestion, is we may need to reconceptualize what it is all about and it would lead to some changes but we have already identified some areas where that change would be needed. However, it might leave others firmly in place and offer additional support. Incidently, this focus on variability may also be one way to capture part of Zeke's concern about community that you have mentioned. So we need obviously -- as we just -- as we work this out and get input from other NBAC-ers and try to determine what will really apply.

Okay. Now those are additional things about information we need. I agree that looking at not only the Canadian model, but also the Canadian draft report is a very good one from last March. We had that in our earlier materials. There are reports of that sort of international nature that we ought to look at as well as the Center for Bioethics, University of Pennsylvania, and other groups that are working on these issues. And I think they can be helpful to us as we are trying to think about this particular perspective.

PROF. CHARO: Do we have copies of the WHO and the CM's?

DR. CHILDRESS: Yes. At least the CM's is in the San Francisco book.

PROF. CHARO: Okay.

DR. CHILDRESS: I think it is.

PROF. CHARO: Okay.

DR. CHILDRESS: Now what would be left out of what we just covered? Anything else that we need to talk about? IRB's? Where do they fall within our part of this? Because we have captured a lot with this --

DR. CASSELL: Don't they come -- I mean, aren't they also going to be considered by the genetics group?

MR. DOMMEL: No.

DR. CASSELL: It did not come up in the genetics group?

MR. DOMMEL: No.

DR. LEVINSON: Well, only in the sense of the fact that they need to be educated about genetics technologies, but not --

DR. CASSELL: Well, we might do well to revisit the

structure -- the history and the structure of the IRB. Because if there are changes to be made they are going to have to be very concrete ones. After all it is in place already. So if there is to be a change, if you are talking about a change in membership then well there already is a membership. So it seems to me that if we are going to do that we have to focus on a meeting or a good half a meeting on it and we have to have background materials and figure out what change we want. It is a sort of -- it is not so much a conceptual issue as the ones you have in front of you.

DR. CHILDRESS: No, I agree. I agree. However, it is one that we need a lot of information on.

DR. CASSELL: Okay.

DR. CHILDRESS: And to think about criteria for priority one might well be what we need to get information on so that we can --

(Simultaneous discussion.)

DR. CASSELL: So we can act on that.

DR. CHILDRESS: So that is one reason for asking again at this point.

MS. FLYNN: Have we not already though identified a concern about the variability although we do not have strong data?

DR. CASSELL: Yes, we have -- that is the point. We have identified concerns about variability, about the lack of training, and about --

MS. FLYNN: Right.

DR. CASSELL: -- a number of those things so we are not talking about structural issues. I mean in the literal sense of structure. And that is why we come back to but we need data. If they are variable what is the data that we have that shows their variability because there has

been research on that. Hasn't there?

DR. CHILDRESS: Some.

DR. CASSELL: I think that there have been studies about that. So we have some background and so we can be able to say, well, this is what was actually shown, this is what we actually know, and that will provide the framework for going on and looking at it, and then we do not have to do the conceptual work that follows from what Arturo has said and what we all said before, which is in some ways more -- actually more interesting. But, in fact, we do need data for the IRB thing.

MS. FLYNN: But the only concern I have, and again you folks know this a lot better, the impression I am getting is that this has been an enormously decentralized system and there has not been a lot of thought about collection of specific kinds of data, and there may not be the level of data or the level of certainty around that data such that we could make the uses of it that we might like to see because we all know that unless we are going to write a whole new system the IRB system is fundamentally in place to guide and protect human subjects. If we want to do something either structurally around the training, the membership, whatever, I do not want us to come up six months from now saying, well, gee, those are all great ideas but we just do not have the data.

DR. CASSELL: Couldn't we come up and say that we have the following ideas, this is the data that is required to bring them in? I mean, we are not -- we know -- we would then know what is it we do not know, towards what is it directed if it is training, why do we need the training. We already have a fair amount of things into which the data set would fit and which would lead to changes rather than what you are

worrying about, which is to say, well, we have the data so let's put it aside for another generation.

I think we would not have to do that. We would have -- we would be able to make substantial recommendations even in the absence of that part of the substantial recommendations being exactly what has to be known, which in itself would lay out how you keep on knowing, an ongoing monitoring of the function of IRB's.

PROF. CHARO: Seconding that notion. To deepen our instincts about what might go on in these kinds of lists though, it is probably worth mentioning a couple of things about IRBs and then asking a background question of staff versus commission because we have not touched on things that Bernie Lo was emphasizing very strenuously and I think that we all noted in our experiences.

The appearance and sometimes actuality of conflicts of interest, whether financial or collegial based on just wanting to get on with another, and the work load problem in combination with the phenomenon of being given recognition and credit for your work within your institution in a way that provides an incentive for the best people to serve for the longest time.

I do not know what there is to help us look at ways in which these things have been tackled. For example, through the use of regional IRB's in certain concentrated settings, which provides some alternative ways of getting around those problems without abandoning the IRB model.

But what I am curious about is whether it is -- most of us are going back to institutions that have some aspect of this stuff or another. And it would not be terribly hard to actually try to interview

people on our IRB's and people who are leading investigators at our institutions and chat them up, and try to develop a more sensitized list of what is perceived -- this incredibly unscientific sampling just to kind of refine our imaginations about what you might want to pay money to have surveyed formally or focus on --

DR. CASSELL: Well, they will be --

PROF. CHARO: -- recommendations, or something like that.

DR. CASSELL: They will be prepared to talk, I promise you.

PROF. CHARO: Well, I know they talk to you now even when you are not asking.

DR. CASSELL: Well, I can see it now. How did you get to a professor? It was all the protocols I reviewed in the IRB.

(Simultaneous discussion.)

PROF. CHARO: Yes. This is kind of what I am talking about. Yes.

MR. DOMMEL: That is the plagiarism factor.

DR. CHILDRESS: Okay. I agree with that effort to stimulate our imaginations in this regard would be an important one. But let me now get concrete in a couple of different ways. We have to -- we will spend a fair amount of time at NBAC talking about our work plan and we need to be clear about that.

I think also we need to think about whether it would be possible, at least from my standpoint it seems it would be very important, to try to get staff to schedule a meeting before our March meeting probably sometime in February. So if that is agreeable with the people here we ought to start working on that so we can make sure we can get a time

where our two absent members can make it also since at least speaking for myself I think it has been a very fruitful time for all of us to interact.

I will say it now since I may forget it later, I think we have been also well served not only by staff, which we expected, but also by our audience which has added very important insights and pieces of information for us today. So we are grateful to you for that. Since my Alzheimer's or whatever is sitting in I will forget that later, but I will mention it now. I wanted to thank you at this point.

So we do have those concrete matters to talk about. What we are going to do with the NBAC meeting and then also working out our plans if we can set up a meeting in February, let's say, prior to our March meeting. It seems to me at that point given what we have gone through today we should have people come in to talk about IRB's, a selected group for that, but also to help us with this -- for lack of a better word -- philosophical reflection or conceptual reflection, the reflection on the vulnerability and all of the issues related to that.

From that note parenthetically this morning I commented that we might follow the model of the National Commission and do our Belmont Report at the end the way they did. Bill pointed out that in conversations he had been involved with, which I think was very useful, that the National Commission did not have a Belmont Report in place to work with. They had to do their own and doing it at the end was appropriate. We have one in place so in effect we can bounce off that.

Even though we have not mentioned that in relation to this notion of vulnerability that we have been talking about it seems to me that what we need to think about also in relation to that is how that perspective

on research involving human subjects would then lead us to modify, qualify, expand the categories that we have been using.

We did some of that this morning in talking about the changing paradigms, but how you think about beneficence or respect for persons or justice differently when you are working this way as a group.

Does that make sense to the group?

DR. CASSELL: Yes.

DR. CHILDRESS: So it seems to me to be part of it as well and I think the suggestion that Bill offered is a good one that we do not have to wait until the end because after all this is already in place. We can react against it -- now we would be reacting to it.

DR. CASSELL: Does that mean we do not have to write as much? Is that what that means?

DR. CHILDRESS: Except that we have to, in effect, write the preamble which is on vulnerability, which in effect is going to be a huge task.

MR. DOMMEL: And you also -- excuse me.

DR. CHILDRESS: Yes. Go ahead.

MR. DOMMEL: You also see that although we have the real change in paradigms, the tension between the principles and the Belmont is not new. It relates now as a result of the continuing tension of what is new and it really does serve as --

PROF. CHARO: Also I think that there is still a question out there whether we can afford to focus attention in the near term on people who are harmed by virtue of not having been included or not having people like them included because of the problem -- the slippery slope problem

and the loss of focus on people who are still being included under inappropriate circumstances.

I still am uncomfortable at knowing when we know when it is safe to move on to people whose harm comes from lack of inclusion.

DR. CHILDRESS: Right.

(Simultaneous discussion.)

PROF. CHARO: Just as a caveat. I mean, I do not reject the notion that the paradigms are changing, I am just -- I am not sure I know what to do with it yet.

DR. CASSELL: You are concrete and you are abstract. It is as simple as that.

(Simultaneous discussion.)

MS. FLYNN: We will have this discussion many times.

DR. CHILDRESS: I am sure we will. Especially as we try to work out this notion of vulnerability.

A couple of other concrete things and then I am going to still come back and ask this again about exactly what we are going to do at the NBAC meeting. Since all of our colleagues, particularly Eric, are excited about being on line, we recommend that the Wisconsin Group's -- what is it called IRB?

PROF. CHARO: Medical College of Wisconsin has an IRB discussion list. Frankly, I do not know --

DR. CASSELL: I am on that.

DR. RACHLIN: It is MCWIRB.

DR. CASSELL: Aren't I on that?

PROF. CHARO: MCW.

DR. RACHLIN: MCWIRB.

DR. CHILDRESS: And the information appears actually in the -- for those -- it appears on page 1626 of the JAMA article from a couple of weeks ago about Institutional Review Boards in distress. So it is in the packet.

PROF. CHARO: Okay.

DR. CHILDRESS: So that is one thing to keep in mind and it has been suggested that might well be a useful way for us to really be tuned into some of the debates going on in that context. I think that is a good suggestion.

Secondly, on the literature side Doris Goldstein was here earlier and had to leave for a dental appointment, and I would just remind you of the library and information services of the National Reference Center for Bioethics Literature, 800-MED-ETHX.

DR. CASSELL: Say that again. What is that about?

DR. CHILDRESS: This is for literature from the National Reference Center for Bioethics Literature and they obviously as a public resource would be glad to help us out in our search for literature. It is 800-MED-ETHX.

Now that gave you an opportunity to think further about what we are going to do at the NBAC meeting.

DR. CASSELL: Well, the structure of that -- what is the structure of the meeting?

DR. CHILDRESS: I have not heard yet, but maybe Bill knows. Thank you. That obviously does shape what we will try to do.

MR. DOMMEL: I suspect the structure is going to be the

morning session will be presentations by one subcommittee and the afternoon session presentations by the other subcommittee, and then followed by discussions and discussions the next morning. The second day is a half day session and runs until 1:00 o'clock.

DR. CHILDRESS: All right.

MR. DOMMEL: Discussions as a commission about the activities of the two subcommittees.

DR. CASSELL: Well then that makes it a little easier on what to do.

DR. CHILDRESS: Right. We have the time frame.

DR. CASSELL: Yes.

DR. CHILDRESS: Well, shall we -- okay. If we were asked to do this tomorrow --

DR. CASSELL: We could it tomorrow.

(Simultaneous discussion.)

DR. CHILDRESS: Right. I will tell you what I would recommend is that we each go back and work on this and try to -- I mean, we are going to take this as a responsibility to -- because I think we have made good progress in getting into this area.

DR. CASSELL: Are we going to get some notes of this meeting?

DR. CHILDRESS: Bill, is it possible? What can we get from the meeting?

MR. DOMMEL: We get a full transcript of this meeting within five working days. This gets loaded to the web.

PROF. CHARO: Great. So it will be accessible through the

web in six to seven working days?

MR. DOMMEL: Right. Yes.

DR. CHILDRESS: But for Eric and me, could you send us a copy?

MR. DOMMEL: Sure.

(Simultaneous discussion.)

DR. CASSELL: Could you send us a hard copy that could be read in strange places in the middle of the night?

MR. DOMMEL: Everyone on the committee wants a hard copy.

PROF. CHARO: Yes, if you could.

(Simultaneous discussion.)

MR. DOMMEL: And the five days also. Okay.

DR. CHILDRESS: Yes, that would be helpful.

(Simultaneous discussion.)

MR. DOMMEL: We sent out at the recommendation of the Genetics Committee a whole set -- new set of calendars. You do not have a set with you, do you?

DR. QUINLAN: No.

MR. DOMMEL: Okay. So blank calendars for January until the end of the school year, June, and asking for what are the dates you absolutely positively cannot come. That is what the chair said. And then -- so that we might be able to schedule meetings when everyone could come.

PROF. CHARO: Yes. That would be great.

(Simultaneous discussion.)

MR. DOMMEL: Okay. So we will do the same thing.

PROF. CHARO: Do the same thing, yes.

DR. CHILDRESS: Okay. You do not have those here now?

MR. DOMMEL: She said that she does not.

PROF. CHARO: Jim, I do not know if it is just the exhaustion factor or just generally, I find it is easier to think through a plan on paper in quiet, but is it realistic among ourselves to be communicating over the next couple of weeks with the accommodation for holidays and the fact that people will be responding after delays, and hopefully give you enough input that you would be able to put together whatever you want to present --

(Simultaneous discussion.)

DR. CHILDRESS: For what we would present. I might kick it off, but this is a --

DR. CASSELL: He is not thinking of the whole thing now --

PROF. CHARO: Well, no.

DR. CASSELL: -- there will be room for you to talk after --

PROF. CHARO: Oh, gee. Thanks.

(Simultaneous discussion.)

DR. CHILDRESS: But that would be good. Why don't we try that for people to send me stuff and I will get it back --

DR. CASSELL: You better then talk about what guides that e-mail. We talked about it at --

MR. DOMMEL: Right.

I think we are still under the initial reaction that I had in regard to the query about availability under Freedom of Information of our e-mail exchanges and that is that they are available and we should regard them as such.

In regard to the agenda for the January commission meeting, understand that I have not had a chance to discuss this with Dr. Shapiro because we were waiting for these two subcommittees to meet, but this seems logical to me given the activities of the two subcommittees.

DR. CHILDRESS: I had a comment back here earlier. I am sorry.

DR. STOKLOSA: This may be imbedded in what --

REPORTER: Would you stand up?

DR. STOKLOSA: I am sorry. Janice Stoklosa, NASA headquarters. This may be imbedded in what you intend to do but I want to emphasize it because it has come up several times with the federal agencies and it is very -- it is important to us.

In view of this changing paradigm the notion of a changing paradigm of what constitutes research. What is the notion of research? And we have the biomedical model which is accepted and understood and has been around for a while. What we are evolving into is we have surveys that are done. We have human factors research. We have research done in operational situations. We have occupational health observations that are done for health maintenance purposes.

So I think that if this committee thoughtfully helped us with a definition, a clarification of what constitutes research, and a clarification of what constitutes minimal risk, that would really help us very much in performing our duties.

DR. CHILDRESS: Right. Thank you very much. I think that is quite appropriate as we try to work out the conditions of vulnerability to get at those issues of risk. But also as we work out the issue surrounding

informed consent, particularly to get at some of these other kinds of research and what kind of consent those evolve would be quite appropriate.

DR. STOKLOSA: I appreciate that.

DR. CHILDRESS: I think that is right. This is what is going to happen when we go back and start tinkering with this, is we are going to see how this is going to take us into this whole area. But I think it could be a very good way to do it. That is right.

Okay. Subcommittee members, anything else you want to add, or staff, before we open this for public comment?

PROF. CHARO: Can we take a break before public comment?

MR. DOMMEL: Well, we may not have any public comment. So then that may be your break. But we have no one signed up at this moment.

PUBLIC COMMENTS

DR. CHILDRESS: Let me just see though if anyone who is here would like to offer any comment at this point. Yes? Please, go ahead.

PROF. CHARO: Stand up.

(Laughter.)

DR. RACHLIN: My notes are so scribbled I apologize. But I did want to make a couple of additional comments about IRB's. Again I am Joan Rachlin. It is obviously a time of very great change and a challenge for IRB's. There are all kinds of hospital mergers going on some of which eliminate IRB's or cause great conflicts as to which one will predominate.

There are certainly take overs by for profits that will call into question the whole issue of research at those institutions. There are

funding crunches about which all of you know. The infusion of industry money about which all of you know. And the consequent change of rules and games, in fact, that these all cause.

In general, there are new areas of research like genetics or like health services, or expanding areas of research that are really throwing IRB's into a major tail spin. They feel beleaguered. They feel unappreciated and they feel quite adrift, I think. And I think that this organization, this group, the NBAC has a lot of potential to really help right them and to really work on issues that have been mentioned around definitions and new paradigms.

I think that having worked with Primer for over 20 years I have seen firsthand what makes IRB's succeed. Again generalizations can be offered. Among them is the fact that they have institutional support and thus credibility at the highest reaches. That translates into money for adequate staff, for adequate amenities for the members, and in general for the kinds of creature comforts and logistical assists that make it run smoothly.

They also really take to heart the notion that there is a trickle down effect in IRB's as with all other institutions and thus a strong chairperson and a strong committee are central to those IRB's which I have observed work well.

Again not to be under estimated is the need for ongoing education. At this point it is mostly informal. But it seems to be that the institutions which succeed send people to our meetings and not certainly to be in any way self-serving about that, but there are many kinds of meetings out there that IRB's can avail themselves of and a lot of IRB's that work

have internal ongoing orientations for new members, and refreshers for existing members.

Similarly those IRB's that fail have no support from the top, thus have no credibility, and thus are treated as and, in fact, operate as rubber stamps. I think that they all want help. Those who run the IRB's are a very earnest hardworking group of people and they really need your support and help because that is where, in fact, their strength will come from or their renewed strength.

I think that there are some suggestions that I would like to very briefly make that again have been synthesized from a number of recent Primer discussions. One, that the model -- the new model of community consultation is a very powerful opening for again this reformulation of both consent definitions in general and the extent to which a new partnership can be created both among IRB's, PI's, and subjects. But between those individual groups themselves. All of that is very, very overdue.

I think that the National Breast Cancer Coalition has done a remarkable job at both organizing and ultimately documenting a lot of this and you would do well to look at their work and to work with women like Fran Visco and Pat Barr in your attempts to see what has worked in a community consultation venue.

Education is key. This concept of extending the requirement to all involved in the scientific enterprise, however lofty and otherwise impossible it seems, is worth exploring. Then there are some very simple albeit politically charged things that you could do. Among them -- in the early '70s George Annas (?) wrote a wonderful bill of rights

for patients in hospitals which the ACLU then adopted and highly publicized.

It has struck me for some time that there could be a corollary subjects bill of rights which could be simple and simply a restatement or codification of the rights and responsibilities of all the parties to the process that could be posted visibly and prominently in all health care facilities, institutions and maybe community facilities as well. Before people have to face these they should be educated about them.

This again would not be any major upheaval. You would simply take existing rights and responsibilities definitions and synthesize and codify them. But something like this would really help subjects, would help investigators, and I think would help enormously IRB's.

I think resource sharing, someone alluded earlier to the fact that IRB's examine these problems in a vacuum, do it with little or no guidance, and again that is where you have large institutions with large staffs, and ample resources doing good jobs and smaller institutions through no fault of their own struggling.

Resource sharing is starting to take hold in research in general. Genetics and biotech, in general, are good examples of those. It certainly could be the case, particularly with resources like MCWIRB, that resource sharing could be much more highly utilized than it presently is.

PROF. CHARO: Resources like MCWIRB?

DR. RACHLIN: MCWIRB, this list server for IRB's, MCWIRB. Medical College of Wisconsin list server. I mean, there are ways to do it. People can just be more amenable to sharing protocols with appropriately whited out sections and encoded data.

Or there can be like in many areas of research there are centers of excellence where ten institutions might each take responsibility for developing policies on a certain set of protocols, cancer and genetics, you know, women's health issues, and share those and informally be willing to share their approaches and policies in those areas.

So resource sharing is an area where IRB's could be enormously -- and it might take nothing more than people saying at the highest reaches you should do this. I think the extension of the Common Rule is a very good idea and something again you might consider.

I think that there is, as I think Dr. Cassell suggested, the need to at least examine ongoing education including certification of both IRB chairs and IRB administrators. Primer is now looking at this and is planning to undertake it perhaps as early as this summer. If not the frank endorsement, then at least a suggestion that some kind of ongoing education would be, you know, useful to the field and we are working in that regard in any case.

And, finally, I think that there are materials like the electronic super highway and the assorted media outlets that exist. So many materials can be shared and I know that Doris has been wonderful, as have other people with data bases, but there should be a way for IRB's, particularly those with limited resources, to access the wealth of materials that exist. Again maybe this commission can place some, however collateral, role in trying to get that kind of coordination going.

But this very basic task of community consultation partnerships, and particularly with respect to consent. I think we are really on to something with the FDA regulation with the work done by both the

gay committee and ACT-UP and the National Breast Cancer Coalition has gotten us off to a very good start in that regard. And then recasting the whole paradigm of rights and responsibilities, and then maybe coming out with something like a statement of subject's rights would be -- again not to under estimate its difficulty, but would be a very great service to all the parties involved.

We would be glad to offer whatever services we can to help. By the way, about the Belmont Report, Harold Vanderpol (?), who is at the University of Texas at Dallas, just did a magnificent talk for us in San Diego on recasting the Belmont Report in the wake of all the changes that research and IRB's have undergone.

I would be happy to make a transcript of his talk available to anyone. He has got a new book which in great depth goes into these issues and I recommend it to all of you.

DR. CHILDRESS: We have a couple of chapters in the packet. I strongly recommend the book too. If I can get the title here off the first page, The Ethics of Research Involving Human Subjects Facing the 21st Century. It is a 1996 publication. It is one of the best works in the area. I strongly recommend it as well. Thank you for mentioning it.

DR. CASSELL: You are wonderfully articulate. I have only one thing I want to comment. One of the things about the rights of patients is it set up in every hospital in this country an adversarial picture of the patient and the hospital. Any --

DR. RACHLIN: I am just citing that as a very preliminary starting point.

DR. CASSELL: I understand that. I wanted to pick up your

comment and go further with it. Instead of it being what this should be, which is the collaborative -- the collaborative role of investigators and subjects --

DR. RACHLIN: I totally agree.

DR. CASSELL: -- which is the same thing said --

DR. RACHLIN: I totally agree. I just wanted to cite the precedent.

DR. CHILDRESS: Yes? Would you identify yourself?

DR. ROSE: Susan Rose from the Department of Energy. I just wanted to add a few concerns and I -- reading over them I sound so bureaucratic. But one of the things I would like you not necessarily to consider explicitly, but at least bear in mind, is cost and who is going to pay for some of the things that are recommended. That is a big problem in our system.

For example, the National Labs get funding from other agencies. If I make a request of our labs I cannot give them anything but my pleading when I ask them to do something or to review something for a small business project in their area. They are concerned about liability. They are concerned about an IRB that meets infrequently coming together to do me a favor for example.

So along with the question the collective burden. The fact that we may be or you may be adding requirements. So are other folks. So that is something that I think should at least be thought about. I would also like to ask if you would consider doing some take aways. Some things that are part of what is on their plate where there is no benefit to the subject.

That is another thought I had which paraphrases somebody named Susan Katz from Yale who gave a talk. When something gets added to the portfolio it should be something that benefits the subjects, not benefits the regulatory community, or those of us who are the federal folks.

So my last concern is we heard all day long about the biomedical model and that is not the one we are talking about in all settings. So when you recommend some of these things, community outreach, some of those things, bear in mind that setting up a one size fits all model is not going to work. So some of these things may have to get targeted to certain settings and they are really going to be a burden where they do not apply.

DR. CHILDRESS: Thank you. Do you want to respond?

PROF. CHARO: Not to respond actually, but actually it reminded me of something that I had come to this meeting and intended to mention. So it follows on. I would love to put on the list of things to explore with regard to the substantive administrative interplay the phenomenon of what you call take aways.

To the extent that one of the problems of IRB's is that they are over burdened and under incentived (sic), you can attack the burden. And I think with the assistance perhaps of OPRR and FDA, both of whom have this kind of experience, it would be interesting to explore realistically whether it makes sense to try and expand categories of things that have either limited or expedited review because I am not yet confident that I understand whether or not those categories have been successful.

I know the way people play games with the categories, but whether also there are substantive abuses that have been uncovered.

And/or the notion of experience rating for institutions and their IRB's in some fashion that would allow for distinctions to be made among institutions with a long track record, over changing memberships and chairs, of being able to keep up the high quality of review and monitoring as opposed to those that are problematic, and being able to reward institutions with reduced paperwork burdens in exchange for them having successfully, you know, leapt over the barrier and proven that through periodic audits, et cetera.

Just to explore these kinds of possibilities so that there is more play than in the system, as well as the creation of new incentives and such. I recognize immediately some of the difficulties of all those suggestions, but I would like to be able to talk about them.

DR. CHILDRESS: Agreed. Any other comment from our audience?

Okay. Commissioners or staff, anything you want to add?

Okay. Well, thank you all very much, staff, and commissioners, and audience. We really enjoyed the exchange today.

(Whereupon, the proceedings were concluded at 3:05 p.m.)

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