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

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P R O C E E D I N G S

OPENING REMARKS AND UPDATE BY

SUBCOMMITTEE CHAIR AND STAFF

DR. CHILDRESS: I would like to call the meeting to order. I am Jim Childress, chairing this Human Subjects Subcommittee. And those of you who have looked at the agenda see that we have a very busy day so that is one reason for starting as early as possible.

I would like to welcome the Human Subjects Subcommittee members, staff, and our visitors today, as well as members of the audience.

One subcommittee member called me this morning, Laurie Flynn, to indicate that she had come down with food poisoning yesterday and would have to miss the meeting today. So she sends her regrets and a few thoughts about the first subject we will talk about, cognitively impaired subjects of research.

I do look forward to this discussion today because we do have a wide range of important topics on our agenda and I hope we can make progress on several of those in moving towards some report that we are thinking about for the fall.

Regarding the members of the public, at previous meeting we have greatly benefited from your input and if there is something you would like to contribute to our discussion please sign up at the NBAC desk outside. We would like to schedule public comments this afternoon for 4:00 o'clock and how much time we can allow for each person will depend on the number who would like to speak.

As you know, some changes occurred in NBAC staff. We are all grateful to Bill Dommel who helped get us started and now he has returned to OPRR. I would like to welcome two members, Bill Raub, who is Acting Executive Director, and Henrietta Hyatt-Knorr, who is Assistant Director. I would like to invite them to introduce themselves more fully and also to share with us any thoughts they have about where we are and where we are going, and how we are going to get there.

DR. RAUB: Thank you very much, Jim. We are pleased to have the opportunity to join you. We recognize the critical importance of the work of the commission and are preparing to do everything we can to facilitate its efforts.

I will be serving as the Acting Executive Director only as long as necessary to complete the recruitment for a full-time Executive Director. We are now drafting the position description for that. We have made certain requests within the administration for the authorities we need. We have been in consultation with Dr. Shapiro and we are hopeful that that advertisement will be public soon and we will have the opportunity of looking at a number of candidates for that position.

In the interim, in addition to my part-time role here I have asked Henrietta Hyatt-Knorr of the Office of Research Integrity to serve full-time as the Acting Deputy Executive Director for the Commission. Henrietta is well experienced in these matters having worked most recently with the Commission on Research Integrity as its Executive Director and has served with me and others within the department as the Executive Director of a number of internal groups, and so brings a considerable experience as well as her enthusiasm to these tasks, and

we look forward to working with you.

Henrietta, any comments you would like to make?

DR. HYATT-KNORR: I am certainly very pleased to be here and I will do my absolute best to help you in achieving the goals that you have laid out already and any other goals that will come up along the way. I feel comfortable that I am up to the job. I appreciate your patience in the beginning while we go through this transition. Thank you.

DR. RAUB: May I just add a comment on the budget front. I know that many of your deliberations early on have been plagued by considerable uncertainties about the availability of funds over and beyond those originally pledged by the National Institutes of Health. In the intervening months at the leadership of Dr. Philip Lee, the former Assistant Secretary for Health, three other agencies of the Public Health Service have committed additional funds for a total of approximately $760,000 from within HHS itself counting the NIH contribution.

Another $800,000 plus has been pledged by six other agencies in other departments, that at the leadership of Dr. Jack Gibbons, the President's Science Advisor. The contacts are being established with those other agencies, agreements are being put in place, funds are starting to flow. So it has given Dr. Shapiro the basis to do some longer term planning with respect to not only staff recruitments but the kind of array of contracts or other support arrangements the commissioners might want and need as you proceed in developing your agenda.

We have developed a preliminary budget with Dr.

Shapiro. He is now reviewing that. We are hopeful by the time of the next commission meeting to have that specified in much more detail and for him to have some thoughts to share with you about particular priorities for expenditure for the remainder of the fiscal year.

DR. CHILDRESS: Well, thank you both very much and again welcome.

Henrietta, would you like to say something about just remind -- I mentioned to the commissioners the sheet you drew up that will guide us to whom we should call or place calls when we have questions?

DR. HYATT-KNORR: Yes. I think it is actually very modest because at this point this is really all we can say because we are just beginning to staff up. Primarily I would hope that most calls are directed to me because I am in the office full-time and it helps me also to find out what your needs are and respond to them.

Otherwise as this particular sheet outlines for various Federal Register notices, back up material, correspondence, responses to inquiry, if I am not in the office certainly Pat Norris can answer that and even when I am in the office you may want to talk to her directly as well.

Margaret does absolutely everything as you well know. She cannot be here today because she is in the office. She is particularly working on travel arrangements, reimbursements, procurements, papers, you know procuring papers. So you can talk to her directly as well.

You all know Joe Mangel and Emily Feinstein. They will

particularly work with the agency responses on the Common Rule.

And Mr. Emerson Randolph Hull, who we also call Randy. That is just about every other support for the moment. We have two other people and a secretary at this time but they are brand new so I think we first have to assign them responsibilities before you can talk to them.

DR. CHILDRESS: Thank you. And I noticed that Rachel Levinson just arrived and there is a seat for you up here.

Is there anything you would like to say as we get started?

DR. LEVINSON: No.

DR. CHILDRESS: Okay. Welcome.

CONTINUATION OF DISCUSSION OF RESEARCH INVOLVING COGNITIVELY IMPAIRED SUBJECTS AND BROADER ISSUES IN HUMAN SUBJECTS RESEARCH

DR. CHILDRESS: Okay. Let's turn to the first matter for discussion today. A continuation of discussion of research involving cognitively impaired subjects.

We had this -- we started our discussion last time with the help of Bob Levine and Rebecca Dresser, and also a contribution in the public comment period from Dr. Shamoo (?) who also provided copies of several papers he and colleagues had prepared.

We want to continue that discussion today with the hope of deciding by the end of our time on this exactly where we are and what we might do next to bring this particular concrete matter filling in a gap in the Common Rule to some conclusion.

To help us in our reflections today we have two persons,

Jack Schwartz, who is Chief Counsel of Opinions and Advice Section of the Office of the Attorney General in the State of Maryland, and who has been the key person in preparing the document that you received back in December, the Interim Report of the Attorney General's Research Working Group from Maryland, which is devoted specifically to research involving cognitively impaired subjects. So we are very pleased that he could join us today for this discussion.

And then we have Jonathan Moreno, a philosopher in the Humanities and Medicine Program at SUNY, Brooklyn, but also involved with the Human Research Ethics Group at the University of Pennsylvania, Center for Biomedical Ethics, which has prepared -- in the process of preparing a document on research involving human subjects, and the draft that we circulated earlier has several pages devoted to a possible draft -- a draft of a possible way of handling cognitively impaired subjects. I understand that is changing some in the report but at any rate he will focus on that but we will also raise some larger questions.

So we will start with Jack Schwartz who will introduce -- set the context for and introduce the draft document that is being developed in Maryland and then we will get Jonathan to focus on the issues as his group has seen in regarding cognitively impaired subjects and then we will engage in discussion with both of you.

Thank you both for coming.

JACK SCHWARTZ, J.D., CHIEF COUNSEL, OPINIONS AND ADVICE, OFFICE OF THE ATTORNEY GENERAL, STATE OF MARYLAND

DR. SCHWARTZ: Thank you, Mr. Childress.

The Maryland Project began as things sometimes do with what seemed like a straight forward question to me. My job is basically to try and answer hard legal questions about Maryland law.

Somebody asked me, "What does Maryland law have to say about research involving people who cannot make their own decisions about research participation?" Initially I thought, 'Well, this was going to be easy because surely federal law would answer the question and, therefore, I would be off the hook.' There would be no need to address Maryland law. And then I discovered to my surprise that, "No, federal law did not answer the question." Federal law begged the question.

So the answer about Maryland law was an imperfect one, that is I advised that Maryland law to the extent it dealt with proxy decision making on the clinical setting could be transferred to the research setting so long as the researching question involves some prospective direct medical benefit to the individual. But Maryland law, like federal law, left essentially wholly unaddressed the question of participation by cognitively impaired people in no direct benefit research. There was not an answer to the question.

That seemed to me to be an unsatisfactory state of affairs. Although I am a bureaucrat I do not really have a lust for regulating everything that I see. But this seemed to be a problem area. It meant that a vulnerable population was to my mind insufficiently protected because the basic form of protection now is IRB review but the IRBs are given no particular guidance or standards here.

It also seemed to me problematic from the perspective of

researchers who whether they know it or not are facing a considerable liability risk. Every time somebody sticks a needle in somebody's arm without legal consent that is a battery. One of these days somebody is going to get hurt and there is going to be a lawsuit and that lawsuit will potentially have a chilling effect, and more parochially to the extent that state employees are involved in such research there is a risk of litigation under federal civil rights laws as has indeed occurred in New York.

So it seemed to me prudent as a matter of preventive lawyering to try and get a handle on the problem and rather than attempting to educate myself and blunder ahead the Attorney General assembled a working group as we label it of about 15 folks comprising researchers, lawyers, ethicists, patient advocates to try and look at the problem.

This group began meeting just about a year and a half ago, met on average every six or eight weeks to discuss the problem, and those discussions culminated in the release of the interim report in October of last year, the document that you have.

That report was distributed to a lengthy, I do not know, 75 or 80 organizations and individuals on a mailing list. We held two public meetings plus another meeting at Johns Hopkins for folks particularly interested in bioethics there. And the process now is that the working group is taking a look at the comments that were received in anticipation of another document and another round of public participation which I will describe in a moment.

In terms of its overall concept or structure the interim report divided research into two familiar categories, direct benefit

research and no direct benefit research. For direct benefit research the basic approach is that decision making involving cognitively impaired people should parallel that which is followed now under Maryland law for clinical decision making. And hence the draft relies on devices like advanced directives, durable powers of attorney, and surrogate decision making.

In general, the reaction of those who commented was to accept this concept. There really was not very much disagreement among those who commented with the notion of essentially carrying forward current law by having the methodology on the clinical side apply to this category of research.

There was a lot of attention paid to an anomaly in Maryland law which is to say that under current law surrogates, typically family decision makers, not agents under durable power but rather surrogates are not empowered to make decisions related to treatment for a mental disorder, a broad removing of authority of surrogates. And in the draft document we simply carried forward that exclusion to the research setting on the theory that one could not have differential standards. That attracted a lot of criticism. I think well grounded criticism. I think in the next go-round we will attempt to formulate some restrictions on surrogates that are less sweeping than that one.

Other comments focused on the question or problem of randomized placebo controlled trials and the extent to which that can really be captured within the concept of direct benefit research, and asked us to focus on that which we have not.

Now within the category of no direct benefit research I

think the basic approach taken by the working group in this interim document is to attempt to correlate evidence supporting substituted judgment with degree of risk. That is to say if the question is, "Well, would the individual if capable of giving informed consent want to participate in this research?" Then the thinking was the greater the risk of the research then the more confidence one ought to have that the answer to that question is yes.

So within this broad category of no direct benefit research the document essentially identifies three subcategories linked to risk. Minimal risk, minor increase over minimal risk, and greater than minor increase over minimal risk. And the authority of proxies to consent to a cognitively impaired individual's participation in research shrinks as the risk goes up.

So to be specific, for minimal risk research the initial recommendation would allow a research agent, that is somebody who is given authority in an advanced directive and the authority specifically extends to research, but allow research agent to give consent, would allow a health care agent under ordinary durable power of attorney, would allow a surrogate or would even allow a monitor where there is an advanced directive to authorize research participation on the basis of substituted judgment. That is for minimal risk.

For a category labeled in the document "minor increase over minimal risk," only research agents or under some circumstances health care agents would be authorized to allow the participation of the individual in the research. And for protocols that involved more than a minor increase over minimal risk only a research agent, that is

somebody who is specifically empowered in an advanced directive to consent to research participation would be authorized to do so with certain oversight by a monitor required.

Not surprisingly, most of the comments that we got focused on this mechanism. There were conceptual, I guess I would label them conceptual comments, at two polls. There were a few commentors who rejected the notion of proxy consent for research participation by a cognitively impaired individual essentially under any circumstances. For no direct benefit I am speaking of now. The position was a perfectly straight forward one, that is not what the Nuremberg Code says and, therefore, you should not do it.

So that the other poll, there were objections that the limitations, the proposed limitations on surrogate authority were too tight. That surrogates ought to be permitted to enroll a cognitively impaired individual in greater than minimal risk research for the sake of the scientific benefits that would accrue through wider research participation. Indeed, there was a comment that IRBs alone in the absence of any surrogate ought to be authorized to admit cognitively impaired individuals in minimal risk research.

So there were critiques that there was too little attention paid to the value of the science that would emerge from some research involving cognitively impaired people and the restrictions were too tight.

There were certainly, aside from these broader concerns, a number of specific comments or criticisms. One, not surprising, had to do with this identification of subcategories, that is minimal risk, minor increase over minimal risk, greater than minor increase over minimal

risk. "What do you mean?", said several commentors. There is, of course, a definition in the Common Rule of minimal risk and the Common Rule uses, the Children's Reg I believe, the concept of minor increase over minimal risk but does not define it. Neither did we in the initial document and we were, I think, rightly criticized for not doing so. On the other hand, to do so will be no small task.

We were criticized, again rightly, for not undertaking an account of the role of assent in the process leading up to research participation by a cognitively impaired individual. There was some commentary over an interesting, somewhat small but still interesting point, which is suppose the individual when competent had participated willingly in a category of research. Now the individual is not competent.

Let's say Alzheimer's has advanced to the point where the individual can no longer give informed consent. What weight ought one to give to the fact that the individual when competent had participated in a category of research?

Should that be decisive evidence of the individual's presumed desire to participate in that kind of research after incapacity? Initially our thought was yes. We were criticized that is wrong, that there is a major difference between somebody who has the capacity themselves to change their mind and having agreed to participate in research and then decide not to, which is the state when they do have decisional capacity versus their inability themselves to withdraw.

There was one specific commentor who criticized the working group for ignoring what he judged to be an important area which is the need for greater disclosure by IRBs as to this kind of research.

That is to say that there is a role for public accountability here that could be fostered by the sunshine of disclosure. And to the extent that we have not included provisions for anything like that, which we have not, then that commentor thought that the document had gone awry.

Let me end by telling you how we see things going from here. We are at the point, that is the working group, of having had now a few meetings to discuss the comments that we received and we will have a few more of those. We will be making public and distributing to the original set of people we sent the first report to and anybody else who wants it another report. Probably my guess is end of April, beginning of May.

So the second document will be an account of what changes we made and why we made them. And it will contain this time not a policy document but a draft statute. As we see it if this process is going to move to anything like a conclusion it has got to move along. So the next thing that we will ask people to react to is an actual statutory text as opposed to a think piece.

So that will be widely distributed. There will be a conference in Baltimore, an all day conference on May 28th to consider this topic, research involving cognitively impaired people in general and the Maryland proposal in particular. So then the working group will once again consider the comments that will have been received in response to the new document and issue, I hope, its final proposal in the fall of this year, the fall of '97.

Assuming that there is something remotely like consensus within our community about this then the Attorney General

will seek to have this law enacted in the 1998 session of the Maryland Legislature which will be in session one year from now. If it were enacted it would become effective October 1, '98. So that is the time line that we are on. That could get derailed, of course, and whether such a law would actually be passed by the legislature is, of course, a wholly unpredictable matter. But that at least is our thinking about what we are going to try to do.

DR. CHILDRESS: Well, thank you very much. Let me just pause for a moment and see if there any questions for clarification before we turn to Jonathan.

PROF. CHARO: Just one. Could you just briefly clarify the limitations on surrogate decision making in the treatment context? You referred to that as the basis for the decision about the limitations in the research context.

DR. SCHWARTZ: Yes. Under Maryland's Health Care Decisions Act, which is a general proxy decision making statute, if an individual is incapable of informed consent to clinical treatment decisions and has no advanced directive, therefore no health care agent or durable power of attorney, surrogates, typically family members, but also potentially friends can make decisions. They are generally empowered to make health care decisions on a substituted judgment or best interest basis. That includes life sustaining treatment decision making authority.

However, one exclusion under current law from the power of surrogates to make decisions is that they may not make a decision or grant approval is the way it is phrased for treatment for a mental

disorder. This provision has been on the books in Maryland since the mid '80s. It reflected, I think, at the time a fear of granting too much power to family members who might abuse it with respect to mentally ill and mentally retarded children or other family members.

So a decision was made back then to simply cut out from the power of family decision makers, surrogate decision makers, authority over treatment for a mental disorder. So assuming people actually pay attention to the law which is not entirely clear, the route that ought to be followed is guardianship for gaining decisions about treatment for a mental disorder.

I, myself, think that is overly sweeping and that one could identify particular matters such as admission to a mental facility that ought to be restricted to a judicial process but that in other respects it may well be appropriate for family members to have decision making authority about mental disorders but that is not how it is now.

PROF. CHARO: Thanks.

DR. CHILDRESS: Other questions or clarifications at this point?

All right. Let's get Jonathan involved and then we will have two models to talk about.

DR. JONATHAN MORENO, HUMANITIES IN MEDICINE, SUNY AT BROOKLYN, AND HUMAN RESEARCH ETHICS GROUP, UNIVERSITY OF PENNSYLVANIA CENTER FOR BIOETHICS

DR. MORENO: Thank you very much, Jim, and thanks to the subcommittee for inviting me this morning, and my special greeting as a former staff member on a federal advisory committee and

expression of concern for the plight of the staff.

I would like to start if I might by making some personal and individual remarks and then sharing with you where the group at Penn seems to be on this subject. I have been interested in the -- in participation of the mentally ill, the cognitively impaired, and research for a long time. In fact, I think my first experience was in 1962 when I was ten years old. I actually had some exposure to some psychotropic research. My father was a psychiatrist who had a small mental hospital on the European model of sanitarium in the Hudson Valley. And I grew up about 80 yards from the hospital, about a 40 bed hospital.

My father was a very innovative psychiatrist and one day a group of -- as often happened -- a group of patients got off a bus from the nearby state hospital, particularly recalcitrant to therapy apparently. And as I often did I started to play softball with them in the field next to the hospital and I heard them talking. It turned out as I confirmed later on that they were there to have psychotherapy with LSD as it was known then LSD-25. I later confirmed the fact that my father had a tax stamp to use LSD in the context of his practice.

For some reason these 15 or 20 young people, and they must have been in their 20's and early 30's, stuck in my mind and a few years later when down the road Dr. Timothy Leary started engaging in his own LSD experiments, they dropped the 25 at that point, it struck me that this stuff had been around longer than people in the general public perhaps had appreciated. And that it actually had been used in research experiments, we called them in those days, you do not call this experimentation anymore, you call it research, for quite a bit longer than

people had appreciated.

And when I grew up and became a bioethicist I learned through my own work that as a matter of fact the psychiatric patients, the mentally infirmed, had been used in research for many -- in many respects, in many ways, even in my own particular interest for national security purposes starting at least with the Second World War.

With this long history it is interesting to read Professor Bonnie's excellent piece that you included in the material for this meeting. It is a wonderful survey of the subject and of the history, and yet it is striking that of all of the scandals, and research ethics is a scandal driven field as we often say, all the scandals in research ethics over the last thirty or forty years we had to wait until UCLA a few years ago to get one for this population. We could have had one much earlier.

Some of you know that in 1953 the tennis pro from the Hudson River Club, Harold Blauer (?), died of a massive overdose of mescaline in the Psychiatric Institute of Columbia University as part of a secret Army Chemical Corps study. That was covered up until 1987 when the Congress gave reparation to the Blauer family. But, in fact, there was no great driving scandal or expose for this population in research ethics.

That, I think, helps to explain why in the lats '70s and the early '80s when the National Commission's initiative to cover this population more specifically fell short, but it helps to explain why it did, in fact, fall short. The fact of scientific opposition is not enough to explain that phenomenon, I think.

It is also, I think, a partial explanation to point out that

this particular group of people we are talking about often have a different socioeconomic status from other research subjects. They tend to -- there tends to be a correlation between poverty and mental illness. That, as a matter of fact, distinguishes it even from some more somatically based or identifiably somatically based cognitive impairment or mental retardation.

And today there is a further complication, just to finish these introductory remarks, in trying to sort out these issues because I, at least, as an observer have perceived a split within the advocacy community for the cognitively impaired, the mentally infirmed, however one wants to call them, between those who are representatives of psychiatric diseases that have more recently been brought under a somatic rubric, for example, such as Alzheimer's, and those who are interested in advocacy for patients with diseases that have not been brought under a somatic rubric. The former group tends to be more supportive of aggressive research in my perception and the latter group less supportive of aggressive research.

Well, these reflections have also led me to wonder what the difference is between a special population and a vulnerable population. I have come to the following operational definition which I will share with you, namely that a special population is a group that is recognized as vulnerable in regulation. This group that we are talking about this morning and that your subcommittee is talking about currently has not been recognized with great specificity anyway as a group that is vulnerable with respect to regulation but I think ought to be.

Now with that -- all those editorial remarks having been accomplished I will tell you a little bit now about the Human Research Ethics Group at the Center for Bioethics at Penn and what this group tried to do for the last couple of years.

The group was funded by the Annenberg Public Policy Center at Penn. It has involved about 25 colleagues from Penn and from eight or ten other institutions for the last couple of years. We have met half a dozen times for two days each. Both catching ourselves up on issues concerning the so-called special populations and also trying to get ahead of the cutting edge as it were of some of the newer emerging issues.

Now since our report is not limited to this particular population but is concerned with considerations of reform of the use of human subjects in general, our recommendations are going to be broader than those that Jack Schwartz just discussed. He put more flesh on the bones than we did.

And our -- I guess the environment in which we operated also was a little different. We were a collegial group not interested in drafting legislation. We did not have to come up with any conclusions at all necessarily. I guess Annenberg would not have been too happy if we did not but we did not have the same kind of drive to address every detailed problem in this area as one does when one is working with and for a governmental panel.

Therefore, what we came up with is what you might call philosophically a kind of overlapping consensus. We did not touch every issue because many of them that we tried to touch we found we could

not get agreement on. But I think that what -- one virtue of the process we went through was that we had a very genetically diverse group in our panel ranging from psychiatric researchers to civil rights oriented lawyers and yet we were able to come up with some conclusions. I say this provisionally because not all the sign offs have taken place yet but I am fairly confident that what I am about to tell you is a serviceable summary of what turned out to be conclusions that represent an overlapping consensus of the human research ethics group.

First in most general terms we seem to be prepared to endorse the notion of expanding durable power of attorney for health care statutes for research involving possible direct benefit to subjects. Interestingly we did not get agreement on the various categories of research that did not present a direct benefit to the subject even for minimal risk research. Again given the collegial nature of our process we did not attempt to push that beyond the point at which we thought it could be pushed.

But at least for research involving direct benefit there was general agreement that those durable power of attorneys for health care statutes, however under utilized they might be, in fact, should be expanded in this direction. Now for research involving cognitively impaired persons including those who are currently impaired or those who are foreseeably impaired, or could foreseeably become impaired in the course of the study, our group seems to believe that the principal investigator should be required to include a written section in his or her protocol that addresses the importance of the research and assesses its risks and benefits for the subjects.

Now while this is often done in protocols involving this population it is not required and our perception is, and the experience of the group as an aggregate, is that this is not always done.

For research involving cognitively impaired persons, whether currently impaired or foreseeably impaired in the course of the study, the principal investigator should be required to include a written section in the protocol that addresses the importance of the research and an assessment of its risks and benefits. It seems reasonable enough.

And to elaborate a bit on that, the principal investigator should also provide a written description of the anticipated subject impairment if it is going to take place in the course of the study. And how decision making for the subject will proceed if the subject is no longer competent. Now this, of course, is under circumstances in which there has been no prior arrangement for a surrogate or agent for the subject. If there has been such an arrangement then that should be recognized or noted by the principal investigator in the protocol.

DR. CASSELL: Would you say the last requirement once again?

DR. MORENO: Sure. If the subject is rendered incompetent in the course of the study the principal investigator should provide a written description of the nature of subject impairment, that is to say if a degree of impairment is anticipated that should be indicated, the nature of the impairment to the best of the investigator's ability, its duration, and how the decision making for the subject will proceed if this occurs, including for example and most pertinent how decisions will be

made to withdraw the subject from the study if the subject is no longer able to make that judgment himself or herself.

We also wanted to say something about IRB responsibilities. In particular that IRBs should be required to determine that the risks are justified as described by the principal investigator and that alternative decision making arrangements as indicated in the protocol are both ethically and legally adequate.

Now those were the recommendations, seemed to be the recommendations specifically for the cognitively impaired but there are some other recommendations that will probably appear in the draft that also relate to this population and other special populations.

For example, the Research Ethics Group strongly believes that a higher IRB priority for this and other populations should be direct monitoring of consent processes, that ways must be found, and we have some suggestions for doing this, to rearrange the way in which paper compliance is assured so that more IRB energy and resources can be engaged in direct monitoring of consent processes, perhaps a kind of auditing of consent processes. We did not recommend consent auditors routinely because there were objections within the group concerning the practicalities involved in such a process.

Clearly that means, sort of parenthetically, to do that kind of -- for an IRB to do that kind of auditing we're talking about ratcheting up the IRB system considerably particularly in terms of the resources that institutions have to -- would have to invest in these bodies, and we have a lot to say about that in the final report or will have.

Also not limited to this population but in general the

report will urge that IRBs be informed of potential financial conflicts of interest on the part of investigators, a growing problem potentially as there is more privately sponsored research as more of it is capitated.

In the regulations currently those IRBs that consider a lot of protocols with vulnerable subjects are already required to include as consultants at least people knowledgeable about the needs of that subject population but we believe that this should be more specific, that this should be specific with respect to the cognitively impaired and other vulnerable populations.

And finally we have a job for NBAC to do. Actually we have several jobs for NBAC to do you will be happy to hear. In particular, NBAC should consider the research group, the research ethics group recommends whether some form of national review should be required for especially sensitive research perhaps on the Recombinant DNA Advisory Committee model.

I guess one example that I had in mind at least with regard to this recommendation for especially sensitive research involving the cognitively impaired could well be research that involves no direct benefit to the subject but some degree of invasiveness or constraint on the subject's movement or behavior and I'm thinking here -- along with some risk.

I'm thinking here, for example, of so-called wash out studies that are combined with the use of spec imaging and other imaging devices that involve some restraints, some physical restraint for the subject, as well as the risk that some symptoms will return in order to do very important research scientifically on the functioning of

dopamine receptors in schizophrenics.

So there are some kinds of research such as research that is sensitive enough perhaps to argue for some kind of large scale public, perhaps even national review process.

That is it.

DR. CHILDRESS: Okay. Thanks, Jonathan.

Before we move into the substantive question are there any questions for Jonathan to clarify?

PROF. CAPRON: I do not know the reason that Eric asked you to repeat the part that you did but both that part and your earlier comment raised a question in my mind that I did not know if I was understanding you correctly.

You said the principal investigator should have a section of the protocol describing the importance of the research and assessing the risks and benefits. I wonder how you see that as different than present requirements. What puzzled me about it was it sounded to me like you were reading from the Common Rule or you presented it as though it --

DR. MORENO: Risk and benefits specifically for the subject with respect to the problems of cognitive impairment. My impression is that this is not always addressed as clearly as it should be. So this is not a recommendation to change the Common Rule. It is a recommendation as it were that IRBs and the research community pay more attention to this requirement.

PROF. CAPRON: I see. And when you say it is your impression, what research did your working group do?

DR. MORENO: The study that I think is really decisive on this score is the research proposal review project from the Advisory Committee on Human Radiation Experiments, which found that there were some significant lapses with respect to this kind of information in a proposal.

PROF. CAPRON: And the other was following up again on the point that Eric asked you to repeat. You said if a subject is rendered incompetent, I think that was the phrase --

DR. MORENO: Right.

PROF. CAPRON: -- in the study and it is the pronoun "in" which I was not clear about.

DR. MORENO: Yes.

PROF. CAPRON: Do you mean by the study?

DR. MORENO: By some intervention, by some manipulation or procedure in the study.

PROF. CAPRON: So you are talking about research in which it would be anticipated that a person who is not now incompetent would be rendered incompetent?

DR. MORENO: Yes.

PROF. CAPRON: And could you give me some examples of which ones you were thinking about?

DR. MORENO: Research involving drug holidays is one possibility for schizophrenics.

PROF. CAPRON: The wash outs?

DR. MORENO: Yes. Another example that has come to my attention is the use of Interleukin-2 which often results in predictable

incapacitation.

PROF. CAPRON: And -- okay. Well, I guess my other questions for you are more substantive. So that was just for clarification.

DR. CHILDRESS: Any other clarification points?

DR. CASSELL: Well, how is that -- how -- I am curious about that rendered statement also. How does that differ from the possibility that a subject will become -- will lose capacity during the course of the research because of the operation of the disease, never mind the operation of the investigator? Is there a distinction made about --

DR. MORENO: No. There is no --

DR. CASSELL: -- prediction?

DR. MORENO: No, from a moral standpoint they are equally significant. But it did strike us that what was learned in the advisory committee's research proposal review, it did not seem to be the case that investigators were taking into account the possibility that procedures that were part of the study itself could render the subject legally incompetent.

DR. CHILDRESS: Okay. All right. Let's open it for discussion then. We have two models that have been presented and some important areas of overlap but also some important differences. Before we -- I do have one actual clarification question.

Could you tell us why you moved away from the fairly specific proposal for additional protections for cognitively impaired adults involved as subjects in research to what I think is a much more

modest statement now. You have summarized some of the things that are present in both. But why did the group move away from a more specific statement?

DR. MORENO: Well, what we tried to do was draft an additional regulation or a subpart and when our lawyer colleagues got a hold of it, I as an editor found it impossible to manage the differences of opinion about the use of language and definition and so forth, and it was a potential nightmare for the poor director of the project. Therefore, I thought there are very capable lawyers like Jack Schwartz, who can do this so we will just tell them what to do. We will not tell them how to do it.

DR. CHILDRESS: Okay. Alex?

PROF. CAPRON: My first question for Jack is to try to get an understanding of how you fit what you are talking about under any notion of substituted judgment. As I understand it, the original use of substituted judgment was to describe a situation in which the person acting on behalf of someone else was entitled to make the decisions which that person would have made which would have caused no harm to the person and the limitation in substituted judgment.

For example, in its original use was that the estate of a person who had become incompetent to make decisions, which that person was him or herself using for the benefit of others, sending a niece to college or something, that that should be continued to be permitted if it was clearly the person's wish. But if the person's financial circumstances had changed in some way so that continuing to be beneficent in this way, benevolent in this way to this niece, in any way

endangered the prospect that the now incompetent person would have money for her own care then it had to be cut off so that the fiduciary responsibility was to protect the individual.

It seems to me within that model no research to which the person has not actually consented which poses anything more than minimal risk could be justified because the whole idea of substituted judgment was you were not to expose the person to any harm but if you have a rich person who was capable of making gifts without endangering her own welfare then that could be continued.

When this was brought into decision making about life sustaining treatment it was brought in as I understand it after sort of a general social consensus had arrived that it was not only not harmful to but beneficial to people who are in permanent comas not to be sustained, that they had no -- they were deriving no value from their treatment. They were, in effect, in a situation in which they could not be hurt or harmed except potentially that their memory and their estate and so forth was being harmed by being continued in this position.

Now people of reasonable minds differ whether that is an accurate characterization of such a decision but the rationale which allowed surrogates to make the decision under substituted judgment, I believe, was articulated by the courts and by ethicists on that basis.

So that even there, even though life support is involved, the argument is you are not hurting the person by stopping life support because they are not getting any benefit from the life support.

Now I do not -- again in other words in its original use and in its bioethics/biomedical treatment use so far substituted judgment it

seems to me has been limited to situations in which the person is exposed to no risk of harm. You seem to be using it to allow either minor or more than minor increase if I understand.

DR. SCHWARTZ: Not as to surrogates, no. In the scheme as proposed surrogate authority to permit research participation for no direct benefit research would be limited to minimal risk research.

PROF. CAPRON: Yes. But the agent who operates --

DR. SCHWARTZ: But the agent -- yes. The agent. Now I think the thinking was that -- substituted judgment is an inaccurate label given its origins. But at any rate the thinking was that if someone, for instance, has written an advanced directive that is specific to research, somebody in the early stages of Alzheimer's let us say, who manifests in an advanced directive a desire to do everything that she possibly can to fight this disease, and writes an essay on her willingness, desire and fervor to do so, and appoints someone as an agent with authority to consent to her participation in future research after incapacity, that autonomy interests seem particularly strong in that circumstance.

So while, I guess nominally, the phraseology would be that the research agent would enroll the individual on the basis of a belief that the individual would have wanted to participate, in fact the evidence would be quite strong in the form of the document. So that whether it is labeled substituted judgment or not it seemed at least preliminarily that honoring autonomy interests, putting to one side the problem of changes in personhood and those issues, but honoring the advanced directive suggested giving the agent authority in those circumstances.

It is -- it was and is more controversial as to whether a health care agent ought to have that authority and that proposition did meet criticism and will have to be revisited in part on the grounds that you are suggesting, that the mere designation of someone as a health care agent does not really tell us much one way or another about the individual's desire of research participation.

PROF. CAPRON: I guess -- and let me preface this by saying that I was very impressed not only with your description of your work but with the effort that has gone into this.

I think this is very commendable that you are doing this and it is in contrast to all of our usual approaches when we become concerned, which is simply to set up procedures, that is to say in New York in the description of the case that you described drew this civil rights challenge and challenge to the use of the statute there, it was basically simply a procedural mechanism. And it is very hard work to do what you are talking about and I do not have a solution.

I do have some further questions about what you have done but I hope I can make clear that I am raising them in a collegial where we are all searching here.

I commend your comment on saying that maybe you should move away from the language which you use and which your document has about substituted judgment because it does seem to me that it is possible to conceive of three different categories of consent being offered on behalf of someone who cannot consent.

One is you are simply implementing what they quite explicitly said should happen here. You are not substituting judgment.

They told you in this circumstance I want you to do this and you are continuing to honor their wish even though they are not expressing it at this moment.

The major issue there seems to me to be do we know (a) whether they would still wish that, I mean because everybody changes their mind all the time about a lot of things. And (b) how do you stop the consent because usually the idea is that we can withdraw our consent and get out of the study, and how do you do that? How do you ensure it?

The second category is the substituted judgment category.

The third category is best interest.

Substituted judgment reflects more a sense of, well, this is the kind of thing that the person would have wanted, never gave me any explicit directive. I know their values. I know how, you know, they have reacted to health care in the past, et cetera, et cetera.

What you are talking about I gather in your research agent is someone who is not just appointed but is given some kinds of directions or not?

DR. SCHWARTZ: That is right. That is how we envision it. Now, of course, a problem is meshing the statement of direction with the particular protocol that is at issue one or two, or three, or four years later post incapacity. The agent's job, and there would be I think some degree of discussion involved, would be to see that there is sufficient match. But essentially you are right that the research agent methodology that we envision is essentially your Category 1. Your

Category 2 of substituted judgment was intended by us to be limited to minimal risk with the exception controversial of health care agent authority for minor increase over minimal risk.

PROF. CAPRON: It has always seemed to me that in the end of life area the instruction type directive is a less attractive document than the agent, the proxy directive because who knows all the things that could happen as we get sick and die and you are much better off having someone who knows well and whom you trust than telling them I want -- this is why I do not like some of those documents that ask you to check off a million things.

DR. SCHWARTZ: Yes.

PROF. CAPRON: That just seems to me it is confusing. All of your work is only aimed from what you have said then at those situations, except the minimal risk, those situations in which you have a presently capable person who is facing the prospect of deterioration because these -- any time you involve appointments you have got to --

DR. SCHWARTZ: That is correct.

PROF. CAPRON: -- you are not talking about court appointment then.

DR. SCHWARTZ: That is right.

PROF. CAPRON: That would be guardianship.

DR. SCHWARTZ: Court appointment is simply bracketed.

PROF. CAPRON: Right. Okay.

DR. SCHWARTZ: It happens or it does not but that is right. We are talking about nonjudicial appointments and, right, competency is of course a prerequisite to that designation. So, yes, we

envision -- since there -- with the possible exception of use at NIH there is now no such thing as a research advance directive. There are few enough advance directives as there are let alone one that addresses one's desire to participate in research of a particular kind.

But the idea would be that if the law underwrote that mechanism then people would be encouraged to use it in anticipation of future incapacity. That is right.

PROF. CAPRON: I guess what all of this raises for me for the commission to think about is what are our overall stance about the balance between research and the advancement of knowledge on the one hand and the protection of subjects on the other.

I think it might be wise if the -- if it were possible for us to distribute Hans Jonas' piece from the Daedelus Collection in 1968 or so, whenever that was, because I do not know whether any of those people who raised objections, Jack, with you about any increase over minimal risk.

But Jonas' essential point is that scientific advance, the advancement of knowledge is an optional goal, whereas the respect for human beings is not. And that when you present -- and I mean anybody -- any of us who have been in this position of trying to come up with something practical take some comfort when we get an equal amount of criticism from the human subject protection side as from the you're shackling research and, you know, stopping progress. We say, well, we must be about right because we are attending -- we are coming up with something which discomforts both groups.

And yet I think we have to ask the question of whether

that is the right perspective in the end. I mean, it may well be that we would be persuaded if we think hard about it that Jonas is right and that there may be some times when at least in any rapid way it is not possible to advance research without violating some very important concerns and protections. And I think we ought to ask that question of ourselves and see where we as a commission come out.

DR. SCHWARTZ: And in the main the proposal does reflect the Jonas' point of view by its limitations contrary to the wishes of some researchers who commented its limitations on surrogate authority. So the debate about health care agents was essentially this: Does the choice -- does an individual's choice of a health care agent reflect such a reposing of trust in that individual that the health care agent's subsequent judgment, call it substituted or not, that the individual would have wanted to participate in research, albeit at an increment above minimal risk, was entitled to special respect or weight.

The initial conclusion was yes and we will have to see whether that departs too far from the limits that we otherwise established on substituted judgment which are limited to minimal risk.

DR. CHILDRESS: Alta and then Diane.

PROF. CHARO: I second Alex's point about the fact that this is an area in which we know that there are going to be mistakes and so the question is which mistakes are you more willing to tolerate, loss of information or an exploitation in the context of research.

I do think, though, that as we heard last time it is important to keep in mind with this population that you have an enormous spectrum of conditions and you have a very early stage of

medical understanding of the conditions and great degrees of variability in the existence of any kind of therapeutic intervention that is given much hope for success.

So that we have here, I think, one of the examples. I do not think it is generally the case but I think we do really have one of the examples of an area in which we need to be concerned both about protecting people from being used as research subjects and about protecting their access to research trials because that is the best place to be.

Secondly with regard to the Jonas' optional goal of scientific advancement, we have got an area in which it is probably important to be distinguished between research that uses people who are impaired for the advancement of general scientific knowledge for the benefit of the entire population and research that is really aimed at advancing information that is relevant to their conditions even if it is not likely to be of benefit to that particular subject.

I mean, I think that there are subareas of knowledge that are of real importance to these populations in the medium term. And so the discussion about the option of, you know, the ability to go without some of these scientific advances I think is more difficult because of the desperate need for some kind of advance.

I mean, I think in some ways it may turn out that some of the ideas that have been percolating in the area of organ transplantation of all places about quid pro quos in which people who are willing to be organ donors are also the ones who will be recipients. I mean, this is under discussion now as a new model for an element of distribution.

We might provide thinking exercises in an area like this in which some people by some mechanism, and I do have some concerns about the practicality of things like durable powers, knowing how infrequently they are exercised in the therapeutic setting. But in some context in which some people themselves or through their surrogates, through their families, are identified as people who are willing to be research subjects both for the kind of basic research that goes to their conditions and to the kind of research that might actually be of benefit to them. The so-called, you know, therapeutic model of research.

And others will be in a much more conservative stance in which they are neither going to be research subjects for things that are not of benefit to them nor to things that are innovative therapies except coming second in line. In other words, the individual takes a stance vis-a-vis the research instead of the regulations necessarily taking a stance is an alternative way of going about it.

It might be worth thinking about because some of these procedural models are just trying to take people who vary from mild depression whose competence is present. But under these rules as written, I know as a lawyer when they are written they are going to look like somebody who is taking Prozac cannot consent, all the way up to people who are psychotic, and it will be impossible to really capture these things properly.

On the other hand I do have problems with the notion of being able to operationalize something subtle because I agree with Alex. Everything you said Jonathan is already required and what you are finding in the review is that the PI's and the IRB's reviewing them were

not operationalizing them.

DR. MORENO: That is right, Alta. But I think that that points to the fact that as we have learned repeatedly in the history of this field and others that unless the enforcement mechanisms are adequate then regulations and principles fall short. So I would want to see the commission not only consider formulations of statutes among the lines that Jack is talking about. But also ways in which the regulatory system itself can be improved.

I do think that on site monitoring, perhaps auditing -- drop in auditing, unannounced visits to the clinical setting and so forth at the recruiting site are very -- would be a very important part of that.

PROF. CHARO: Jonathan, just by way of clarification on this. This is the -- I am pointing to something you cannot see. This is the research protocol review project that you have there. When you went through these 125 protocols were they all from sites that are currently regulated because they were either using FDA --

DR. MORENO: Yes.

PROF. CHARO: So do you have any basis on which to comment on the different experiences in unregulated sites and regulated sites?

DR. MORENO: Only anecdotal, unlike yours, my hunch is that, you know, things are at least as ragged in those places but it is anecdotal. By the way I would say that one of the concerns of the Human Research Ethics Group also for -- perhaps for the advisory commission would be to either undertake itself or to recommend a systematic study of the economy and extent of the current IRB system.

That is to say how many IRBs are there? Where are they?

Should they be registered and so forth? You have heard this before I am sure from others who have visited you. But also how much is invested in the system? With institutions charging up to what, 62 percent overhead, it would be very interesting to know how much they actually spend in support of their human subjects review apparatus that could conceivably be funding that would facilitate kind of more direct monitoring that I was talking about before.

DR. CHILDRESS: Diane?

DR. SCOTT-JONES: I have a question, Jonathan, that is related to what you were just saying and that is how IRBs function. When you were speaking you mentioned that IRBs should be required to determine whether the risks are justified and I just wanted you to say a little bit more about the extent to which you actually mean that because doing that to any great extent would mean that IRB members would need to make judgments about the scientific merit of the study that they may not be prepared to make.

They may not be prepared actually to undertake a risk-benefic calculus for the range of research that they would be required to review. It seems to me that IRB members might not be prepared to think of alternative less risky research that might be done in lieu of a study that is proposed to them and they would then rely on the persuasiveness of the research or on the reputation of the researcher.

Could you just say a little bit more about --

DR. MORENO: Everything you say is true. My experience in an IRB, and I believe this is not unusual, is that IRBs tend to fall back

on the view that all we are here to do is worry about consent when they do not think they have somebody in the room who can really speak authoritatively about the substantive research. But that when they do have somebody in the room who can speak substantively about the research that is being proposed they are quite prepared to get into methodological questions. And if that impression is accurate then it seems to me there ought to be some way to ameliorate this bouncing back and forth.

While it is certainly true that they must be concerned with consent methodologically and adequate research is also bad research in some kind of normative sense. So I think that again if the IRB system were better supported it would be more possible for the IRB to operate in a way in which it would have more expertise from either from its own community or from another community to help it evaluate the risks and benefits associated with the particular study.

I do not think that the general public is going to be satisfied if the IRB community, whatever that is, says, "Gee, we are just talking about consent here. We are really not in a good position to decide whether this principal investigator who has this multimillion dollar part of a multisite study perhaps, multimillion dollar contract or grant, is really accurately representing what he or she has an interest in seeing gets approved and gets further funded." I do not think that is going to fly with the general public. I think the public expects that we as members of medical school faculties, the scientists and scholars are in a position to do peer review which is what we are supposed to be doing.

So again I think that the nuts and bolts of the system

itself, as unsexy as it is, compared to the philosophical problems really need attention very badly.

DR. CHILDRESS: Eric?

DR. CASSELL: Well, but that last point is really -- that is really crucial. You know, that is like saying, "Well, it looks good in theory but it does not work in practice." The theory is either right and it works in practice or the theory is wrong.

One of the things that I am brought to in all of this is back to the Hans Jonas' point. It is very hard -- I mean, information seems to have a power of its own. It is as though it lies there under the ground trying to push its way through like grass through asphalt and you are just waiting and it is such an essential thing to go get that information because -- but that is not the case at all. Information is not doing any such thing at all. The push is not in the information. The push is in the person's mind who is out after it.

The educational process required here to understand that the thing you are after as a research person is second to your interest in that subject's well being. No regulation in the world up until -- I mean we would not be here if regulations alone solved that problem. We would not need to be here. No regulation alone is going to change the difficult position that we find when patients have varying capacity because the very fact of the varying capacity is generally primarily known to the research person, not to anybody else. And that research person's responsibility for their subject has to be overriding.

Regulation does not make that the case. Although regulation is absolutely essential and it sort of provides the subplatform

from which everything else goes. Regulation is a kind of information itself. Regulation is a kind of education itself. But in and of itself -- venality is widespread and never gets solved by regulation. What we are talking always about is the people who are doing things who are good persons in truth and ride over their subject's well being. That is our primary concern.

So as I listen to this and think back over 25 years of listening to this problem discussed and trying to think what are we to do that is going to be different, which I think I hear, you know, a difference in the Attorney General's conversation about this. There is a distinct difference from 20 years ago and trying to see it somewhat differently and trying to understand --

DR. SCHWARTZ: Better or worse?

DR. CASSELL: Oh, I think it is a lot better. I mean, we all understand how difficult it is. But for us as a commission trying to figure out, well, what is the next step, I do not believe the next step is another layer of people hovering over the research site who are going to make sure that, in fact, you just did what you are supposed to. Though in fact there may be times when that is necessary.

I am not saying -- I am not naive about what people do. I am certainly not. But I just do not think that that is the fundamentally new way to solve problems, is to put another -- to put another investigator on site to investigate the investigator's investigation of the subject.

PROF. CHARO: So what are you proposing?

DR. CASSELL: Well, as I hear it --

DR. MORENO: I thought we were agreeing.

DR. CASSELL: What?

DR. MORENO: I thought we were agreeing at the beginning of your remark.

DR. CASSELL: No. We are agreeing about the problem.

DR. MORENO: Okay.

DR. CASSELL: We are not agreeing about the solution.

You know, I have said from the beginning that I believe that one of the things we have to see differently is that we are not talking about two opposing armies clashing at night or in the daytime. We are talking about people who have a common interest and how to solve the problem that one group against -- that we are not always seeing versus. That we are trying to solve the problem of -- I think the answer is actually an educational one. Then ultimately we are going to educate investigators not by some template that is stuck on the outside, they take an hour course.

We are going to end up truly making it clear that part of knowledge is the subject. Knowledge is not separate in the subject -- you know, like a peanut with its hull. You take that and throw the hull away and you get the knowledge. Knowledge and the subject are inseparable. Respect for one is respect for the other.

Now you can say, "Oh, you will never get that." Oh, yes, we will. I remember when people used to lie and cheat about their consent forms all the time. Now they only do it about 10 or 15 percent of the time. So, yes, you get somewhere but you do not get somewhere by just saying, you get somewhere by figuring out how, in fact, are you

making investigators understand the nature of their research, just as the general public has come to want to be a part where the action is.

Alta, that is what you are really saying. If you have got a bad enough disease, particularly one that puts you outside the community like these do, you want to -- you want to be part, you want to be better even though the history of therapeutic research in psychiatric disorders is hardly a history of outstanding success.

DR. MORENO: Can I just add there, Eric, I do not think that what I was suggesting was an adversarial process. It is highly unlikely that my colleagues in the IRB would send an adversary down to their colleague in the Department of Medicine in an adversarial way. But the reality is that many times, in fact most of the time, the people who are doing, for example, the consents are a relatively low level in the hierarchy in the medical center, and they may not know what the hell they are doing and they may not know how to explain the nature of the study in lay terms.

It seems to me that those people do need some help. I think we are probably closer together than I was able to articulate before.

DR. CASSELL: Well, then right away we might say that that is not the person to obtain consent from.

DR. MORENO: Well --

DR. CASSELL: Right off the bat we might say the consent process is like --

DR. MORENO: Right.

DR. CASSELL: -- medicine --

DR. MORENO: Right. I agree with you. Then the IRB should be able to go back to the PI and say, "Look, you have got a problem at this level in your process that we have identified. Just sitting in on two or three of your interviews in one day we found it at your site."

DR. CASSELL: Yes, I think that is correct. I do not think that is quite what I -- I do not think that is being a --

DR. MORENO: Right.

DR. CHILDRESS: All right. We will take a couple more points on this and then I wanted to press us to where we go from here as a subcommittee. That is what we do next in this particular area since this is one there is a general consensus there is a gap that needs to be filled.

We have heard now in two different sessions from people who -- last time from Levine and Dresser and Dr. Shamoo, who addressed certain points, and now in a more specific way two proposals from two different groups. So I will be pressing us to move and decide what we are going to do next in order to bring closure to this.

Alta?

PROF. CHARO: I find myself thinking about Jonathan's suggestion that we think about the implications of a national IRB or regional -- collection of regional level bodies that take on topics like this for the following reasons:

Diane's observations about IRBs and what they do or do not feel free to do were quite at odds with my observation of the IRBs I have worked with, which only points out the variability. But being on an IRB that actually does, in fact, try to do risk-benefit review for all of these

we have run into the difficulty of staffing it with the appropriate levels of expertise, turnover. We have turned into a place that now has prereview by department heads and department groups for areas where we cannot get appropriate experts, da, da, da, da. We have been struggling to do this.

Now knowing how hard it has been at a place that is well stacked with researchers from every field, we have been fortunate that way because we have got a full fledged research center, and then hearing about how variable the experience has been at other places, the prospect of adding on the need for education on this kind of problem of how to approach even suggesting involvement in research to people whose ability to make decisions runs the gamut from almost completely intact to virtually gone and are sporadically moving among those levels.

It strikes me as a project that might succeed in the end, Eric. I will not tell you it will never happen but it is daunting in the extreme. And it makes me think that there might be room for identifying certain subtopics in which there is a need for a group that worries about certain things more consistently and that there be certain trigger factors, for example something that is not likely to be of benefit to the subject himself or herself, or something that does entail more than a minor increase in minimal risk, whatever that turns out to mean, that would generate a presumption that it cannot be done until it has been cleared through a regional or group body, or something like that.

Now this could be unwieldy. It could be ungainly. But it is something that probably does deserve some discussion because the attempt of going at it substantively and protect both access to innovative

therapy in the form of research trials and protect people against the much more frequent problem of exploitation seems impossible because you cannot write a single set of rules that will cover both situations. They have to be handled in an ad hoc fashion.

Decentralized, individual IRB efforts to implement that ad hoc set of rules seems like it is destined for difficulty in operationalization considering what we have got going now.

DR. CASSELL: I agree with that. I think, in fact, what you are suggesting is when you move up a level in an IRB you are moving up a level in expertise. The IRB represents an expertise in trying to balance the needs of both the investigator and what is to be done to protect. And that expertise is an educated expertise. So I think that is --

PROF. CHARO: Well, more or less depending on how long they have been serving. But you can imagine, you know, special areas of specialty expertise. For example, imagine you are fortunate enough to be in a metropolitan area with multiple centers where when these kinds of subjects are going to be enrolled there is a subcommittee made up of people from IRBs from various institutions around the city. This is all consistent with current regs anyway. It does not take any change. Who meet periodically to work through these protocols only because of only this aspect of it and then serve to feed back into the individual institutions and their IRB processes.

DR. CHILDRESS: And we are going to come to the IRBs a little later in this period before the break. This is one change in the agenda because Charles McKay has been able to join us but has to go to NIH as do both Jack Schwartz and Jonathan Moreno. That is why we

have worked them in early this morning. So we will turn to IRB studies and what else needs to be done in that particular area later in this session.

So if it is all right with the group I would like to push us to bring this to a close today as to what we want to do next in the area of cognitively impaired subjects. And even that label, I think, is one that need some closer attention, whether decisionally impaired subjects would be broader and encompass those who are suffering from emotional rather than strictly cognitive problems. That may well be one thing that needs some attention.

Laurie Flynn, who very much regretted she could not join us, indicated two things. One is that she very much likes the direction being taken, not that she was accepting every single thing, but very much likes the direction being taken by the draft report in Maryland. And, second, thought that Richard Bonnie's suggestion that we not try to develop something for a variety of groups but rather decisionally impaired generally. That we try to work on that level. Those were two points that she wanted to underline.

But my bit question is where do we go from here? Are we at the point where we could through a couple of members, presumably Laurie and someone else, try to pull together what we have covered and see if we can come up with something that we would like to recommend? If so, at what level of generality or specificity should we operate? Or should we try to go to a contractor on this? Or should we -- our staff may not have evolved to the point where we have someone who could take this on.

Another thing we are certainly going to need to do is hear from both researchers and patients in this area. Is that better done at the point where we have a draft to work with and get feedback? Or is that better done earlier?

Those are just some of the questions we need to address but this is one area given our consensus that there is a gap that we need to close where I hope we can make some progress over the next couple of months.

Alex and then Eric?

PROF. CAPRON: I have raised with you before a question, which as I said to you then I was not clear because I have my own reference library of materials, whether we had had distributed to us as a commission the 1978 report and the draft HHS regulations, HEW then, regulations which were not implemented?

DR. CHILDRESS: I am not sure we have. I have -- like you, I have a copy and I suspect some others do. But I do not --

PROF. CAPRON: And it would seem to me that at a minimum we ought to carefully review and perhaps with the aid of the memories of those people who were directly involved, Charles McCarthy was probably one of them, if he is available to aid us in that, what that process was and some depth into what the objections were. Obviously we would reach our own conclusions about the merits of those regulations. But this is not a process, as Richard Bonnie reminds us, that we start at ground zero on and we might as well not go through something that has already been gone through.

So I would suggest that those be distributed as soon as

possible if they have not already been.

DR. CHILDRESS: Let me just thank both Jack Schwartz, who is leaving the room, and Jonathan Moreno for joining us. And you are welcome to stay, Jonathan, as long as you like. But thank you both very much for this helpful discussion.

DR. SCHWARTZ: Thank you.

DR. CHILDRESS: All right. Alex's suggestion has been, I hope, duly noted on providing those two and then also the suggestion about having some discussion perhaps with Charles McCarthy about the process.

PROF. CAPRON: That is just one name. There may be other people who are equally appropriate.

DR. CHILDRESS: Okay.

PROF. CHARO: Following along with that, this reminds me of where we were when we were ending up last time because we did have a discussion of what the objections were at that time. I remember inquiring what the problems were now because we need to know what the obstacles are now to moving forward. So if what I am hearing is a suggestion of taking those old regs, the old draft of the regs, as a starting point and then saying what is wrong, what is good, what needs to be amended, et cetera, it would seem to me that it would be valuable if we could at this point elicit whether it is written or in the form of, you know, verbal testimony.

Comments from the people who are involved in the major organizations of both researchers and patient groups and their families on those regs -- I mean, essentially it is a recreation of what happens

when you publish a Federal Register notice and you invite comment because unless we get a handle on why people today do or do not like those regs we are not likely to be successful at steering through them to a solution that is acceptable.

DR. CHILDRESS: I think that is right and I think we can certainly do more with some of the participants involved. I would note that Robert Levine's work and also Richard Bonnie's work, both spend a fair amount of their articles trying to lay out what was problematic about those, why they were considered controversial, and also what has changed since then, and why it is important to move beyond the kinds of categories that were used at the time both because they were controversial at the time but also because things have changed so much since then as to render them even less appropriate. So we have some of that already before us but there would be no reason why we could not do more with some of the participants involved.

Okay. But where else do we go from here?

DR. CASSELL: I would like to hear what some of our own committee members, like Laurie, has to say before we go out, too far out, because of their experience in the whole issue.

DR. CHILDRESS: Right.

DR. CASSELL: I -- so we have a little more basis when we begin to listen to contract people talking about what we want to actually write.

DR. CHILDRESS: Okay. And I reported what she -- she regretted she could not be here to amplify this morning.

Alex?

PROF. CAPRON: Yes. On a substantive matter you reported her as saying something that was very different than what Alta said a few minutes ago and I agreed with Alta and I want to see if I understood her comment, Laurie's comment in absentia.

She -- in your version -- was saying, "Let's not highly differentiate."

DR. CHILDRESS: No. Let's not try to develop categories. Let's not try and develop guidelines for -- well, basically Bonnie's argument is let's think about decisional incapacity generally. People who suffer from that.

PROF. CAPRON: And she was agreeing with that?

DR. CHILDRESS: She was agreeing with that. That does not mean, though, that you would not then draw some lines and talk about people who have the capacity to consent or those who have the capacity to assent or not consent and so forth, and there are lines drawn, but not to draw them in any kind of disease or illness specific way.

PROF. CAPRON: I mean, I did not take Alta to be saying disease by disease.

DR. CHILDRESS: Right.

PROF. CAPRON: But to recognize that we are talking about a gradation of --

DR. CHILDRESS: A gradation of decisional capacity/incapacity.

PROF. CAPRON: Well, it may be -- there may be differences also between chronic conditions and episodic conditions.

There may be differences between progressive conditions and in-born conditions, et cetera. And one thing that occurs to me, of course, is that the national commission's report and the HEW regulations dealt with those incapacitated who were institutionalized.

DR. CHILDRESS: Institutionalized.

PROF. CAPRON: Which is yet another differentiation and obviously despite Jonathan's comment that this sort of began only recently with the UCLA experience, many of the early horror stories of those being ill treated were precisely those who were institutionalized, the Willowbrook experiments on the mentally retarded, the -- even the Jewish Chronic Disease hospital case, although it involved cancer research, was on cognitively impaired, demented mostly, elderly people in the hospital. And so the exposure of people in institutions, particularly total institutions, who are mentally incapacitated may be very different than those who are ambulatory.

DR. CHILDRESS: And again starting in that general way is --

PROF. CAPRON: So these --

DR. CHILDRESS: -- does not mean that one would fail to attend to that difference.

PROF. CAPRON: Right. I just wanted to be clear that we were not.

DR. CHILDRESS: But that was one of the mistakes many argued in retrospect that was made in the initial was focusing on the institutionalized, which may have been every more appropriate at that time prior to the -- or at the time the HEW regulation was occurring. But

at least now to focus on decisional incapacity and then deal with these variations starting with one of the subsets and making that the sole part of reference for policy and regulation.

PROF. CHARO: Jim, going back again to what it is that we can be doing. I feel like we are circling over and over again about the mandate question. But we could be working at a very high level of generality or we could be working at the level of almost regulatory detail.

At the level of high generality we could choose to try to answer the question that Alex put which had to do with the basic direction that you want all regs to go however they are drafted and by whom to err on the side of being protectionist against exploitation to err on the side of generating knowledge with appropriate safety hatches in both directions so that you do not have a rule that is so rigid it shoots itself in the foot.

Now you know that there is a great deal of merit to the notion of -- that has been widely shared by a lot of the writers we have been reading -- of presumptive prohibition on research that poses any kind of physical risk or emotional risk to people who are decisionally impaired simply because there is no basis on which we should be permitted to judge them or judge ourselves as being appropriate representatives to say, yes, for them.

And then the question will be what kind of escape hatch do you create so that you do not have therapeutic orphans? So that you do not have lack of access to things that are of immediate personal benefit? And that is where you would begin to worry about national bodies or regional bodies or every IRB subject to certain kinds of rules,

et cetera. But that the level of generality at this commission level could start with, and I am not advocating it, but could start with a decision about whether or not to say whatever happens, whoever does it, they ought to start with a general prohibition followed by exceptions.

That ought to be the model for working with decisionally impaired people because that is protectionist and if there is anything we know it is the history of abuse because -- or we could -- we can obviously have the opposite and say scientific research here is so crucial that, in fact, it is the one area where you want to push forward and you would want to say the exception ought to be when you cannot do the research in each direction.

We could be working at that level of generality and it is worth deciding whether or not we think that has got any value to anybody before then moving to the -- because you cannot come and work in the middle. You immediately then work at the very detailed levels where I was talking about Federal Register notices, regulatory stuff, because the intermediate level of specificity gets into questions of whether or not you could operationalize it and that then gets into questions of such empirical depth and with such change -- you know, fine tuning of procedures that you wind up working as a drafting body.

DR. CHILDRESS: I guess one question would be -- notice that the Maryland group is now moving towards drafting legislation and they considered the document we received as a policy document. That I take it is still too specific from the standpoint that you were raising because it gets into the operational questions.

PROF. CHARO: For example -- yes. Because, for

example, I would have great difficulty raising my hand in support of the notion of durable powers of attorney for research. I find it a very troubling operational detail. So I would hate to be forced to have to say yea.

DR. CHILDRESS: No, I mean I was not recommending the Maryland statement because obviously --

PROF. CHARO: Right.

DR. CHILDRESS: -- we would have to -- the question is whether -- again trying to determine the level we want to operate on and I am just trying to determine whether that is too specific for you because a lot of these matters we will just have to hash them out as to whether we --

PROF. CHARO: Yes.

DR. CHILDRESS: -- get agreement on a particular area or not.

Other comments about how to proceed because I have a feeling -- again I have -- from our previous conversation that this is an area where we think we can do something and the question is given our time frame, and you did receive a schedule of meetings though we obviously are going to meet as a subcommittee before that, but where do we go from here? What do we ask for next? We have already had a couple of suggestions. But what else?

Again are we at the point where we could -- do we want to try to resolve this question that Alta has raised before we get people either on the staff or outside or on the commission working on these matters? Where do you want to go?

I guess my sense was that there seemed to be enough to work on building on what has already existed that if we could settle some of the general things just sort of establishing the direction then we could go ahead and get, again one of the three, groups I mentioned working on something that we could discuss in more detail. But we are going to need input from actual researchers and patient groups along the way either before or as we engage in the process of drafting some kind of statement.

My only point is that if we cannot move forward in this particular area then I am not sure how much hope we have for a report by October because this is one of the most thoroughly plowed areas in the last couple of years.

PROF. CHARO: Jim, one possible thing that we could do that is very concrete is we could actually -- we have already got many of them, gather the existing specific drafts. If you want to try to work at that level, right. We have got at least two that have been given to us. There are five or six that have actually been published, complete drafts, not policy statements. You can line them up. We can work through them. We can use them as the basis for the comments that we request from other groups. We could choose to endorse one of the others or none of the above and that would be the outcome.

I do not know if you -- if I am sure that would actually satisfy what we are hoping to do but it probably would come very close. How we evaluate them is still kind of up for grabs because we do not have a -- we do not have a consensus about direction. I personally am kind of ambivalent about the direction. But even so it would be

something to start with that is concrete.

DR. CASSELL: Alta, why are you ambivalent? I mean I am too. But why are you ambivalent about direction?

PROF. CHARO: Because I think we need the research in this area desperately but every time I get confident that we need it so desperately we should go ahead and move forward we have another outbreak of some tremendously outrageous abuse of people's dignity and their rights that comes to light in some particularly institutionalized setting. And my introduction in this whole area, indeed, was the Willowbrook business which took place very close to my back yard.

DR. CASSELL: But it is that same problem. Is the regulation to be based on the -- I am trying to think of a good adjective for it -- bad behavior of a few or is it to move forward in the large majority of investigators who are not inherently --

PROF. CHARO: I know. It is --

DR. CASSELL: What do you think?

PROF. CHARO: How many hamstrung investigators equals a group at Willowbrook that was just abused like crazy? I do not know how to put numbers to those two things.

DR. CASSELL: Well, which do you think -- let me put it differently. Do you believe that if you can find a way to write it so that there will not be somebody who sneaks in and does bad things to other people who will have to be protected? Do you think you are going to be able to do that?

PROF. CHARO: I think that a motivated person who wants to lie, cheat, steal and manipulate can always lie, cheat, steal or

manipulate. You cannot write a procedure to prevent that. The criminal justice system gets as close as you can get and you see how cumbersome that has become as a result.

However -- and this is why I was asking about generality before we talked about debating specific drafts. I do think that a different model other than the regulatory drafts that we have seen so far which attempt on substantive criteria to tackle the question of what can be done, by whom and when based on the risk at hand and the benefit at hand, et cetera. I think an alternative way of going is to say you cannot do it on a more general basis like that. It has to be ad hoc.

The system for ad hoc review we now have with the IRBs is probably not capable at this point for whatever reason of operationalizing this in a way that we are confident will prevent Willowbrook. So the question becomes is there some alternative way of handling it through regional or national level review, through a different body that is devoted to this, that is made up of people who then take this on as their -- you know, as their purpose which is to make sure that these kinds of protocols only go through when they are being done properly so that the investigators both can do the work that they want to do without a million IRBs handling it under different standards as they interpret standard language.

This is an alternative way of going about it. But it is the creation of another level and another body and that has --

DR. CASSELL: Yes. So the answer to the question of why you are ambivalent has to do with the occasion of Willowbrook. I am not minimizing the importance of the Willowbrook. And your solution is if we

put that aside you believe that we could address the question, directly address the question of another level IRB or an equivalent, and that that would be a productive thing to do.

PROF. CHARO: I am throwing it out for discussion. I am willing to be persuaded in either direction.

DR. CHILDRESS: And that is the discussion we will have to have but at another time.

As I said what we have got to do now is decide on what we are going to do in order to have that and resolve that discussion. So a couple more points and then I will try to summarize where we are.

Arturo?

DR. BRITO: I agree with Alta's comment about you cannot prevent somebody that willfully wants to do harm from doing harm. One of the things that I would like to hear aside from the families, et cetera, that have been the victims of scientific research is I would also like to hear from some of the researchers and this is possible to have done.

For instance, from UCLA, that have also been the -- that have not -- that have been perpetrators of abuse in these research, but have maybe not felt at the time that they were doing the research because I would say 90 percent of the time even going back to the Tuskegee Syphilis experiments the people doing the research did not feel at the time that they were being abusive.

And I think it is important -- it would be important to hear from that side and I think that would give us some direction on where we can go because I think as a scientist -- scientists will sometimes feel that

the acquisition of knowledge in an immediate manner, whether or not it would be deceitful or whether it would be perceived to be deceitful is more important at the time than the patient's rights. So I -- or the subject's rights in research.

So I would like to hear from that side in addition to the families if it is possible to get the researchers in here.

DR. CHILDRESS: Alex?

PROF. CAPRON: I think we need someone to do or maybe some ones to do a couple of things for us. One is to explore in some detail and with an eye to what it would mean, along the lines that Alta has suggested and so forth, taking the different perspectives. I mean, the articles that we have seen from the Cleveland Plain Dealer I was struck by a number of the comments there on the Veteran's Administration studies.

And at the end of the article of February 16th by Bill Sloat and Keith Epstein there is a quote from a Kristy Ann (?) Teleson, a practicing psychiatrist and director of forensic psychiatry at the University of Maryland, and this is along the lines of what Arturo was just saying. She said that the main risk of withholding medications from a mentally ill person is "that the symptoms can come back or relapse," and then the authors go on and say she said, "Psychiatric researchers face complex ethical issues because 'you have to have a control group to study.'"

I am sure that what she is, in effect, saying is that these people think they are doing a good thing and yet the requirements of their own scientific disciplines push them to do something which then

results in what to those of us on the outside appears to be a scandal.

I agree with Arturo. I think we should hear some of the justification. But we need someone to think through the implications of the alternative perspective and put us in a position of then saying to the world if we were to say that research is always the secondary and never the primary objective in the interest of the research community, and despite the value to people who have the diseases themselves of having further understanding of those diseases that has to take a back seat and that would mean the following, and then put that out there sort of see who shoots at it and what they can tell us, whether they are a researcher or a member of a family, or an individual who has been treated for one of the conditions that would be involved, and really get some purchase on how contentious and how troubled we would be in taking that strong a position.

So that is a conceptual work that we are going to need some help with it seems to me. And obviously someone like Jay Katz or someone who has thought deeply about research could be the kind of person one might think of turning to. There are others I am sure we can all suggest.

I also think we need an analytic framework and someone -- and this is something we need a staff person to develop or a contract staff person to develop an analytic framework for us. We have heard suggestions already that one way of breaking this down is by categories of the potential subjects.

I want to ask first of all whether it makes any sense to distinguish between subjects and patient subjects. There has been

argument here or use of the term "direct benefit research." I am very skeptical about that terminology. And this quote about the need for the control group underlies it. I mean any time you have a study what you are saying is this is research on your condition and the purpose of the research is to test out some method of treatment of your condition.

Now whether that should be called direct benefit research and distinguished from nondirect benefit research is a basic question particularly if one of the ways we study your condition is to give some of you the known effective treatment and some of you the placebo to make you the control group or some of you something else. I mean, in what sense is that expected?

The whole notion of the null hypothesis which starts off by saying we do not know if this will do any good to you at all. But maybe there is some argument that there are maybe three categories, that which is directly implementing a new research methodology where it is like trying out AZT on patients with AIDS and people desperately think this is the only available treatment and has shown some initial good and the only way I am going to get it is to be in the research.

And then there is this category where you are doing a true controlled group and you might or you might not. And then there are those things where it is just adventitious. You happen to be a mentally incompetent person who is in an institution and we want to study your condition but there is no intention of directly benefiting you at all. It is just that we need to know more about the condition or you are an available subject.

So those -- I would like to have some examination of that.

I would also like to have us look at different categories in terms that you raised, Jim, of competency. Those who are presently competent. And here we could distinguish between those who were institutionalized and those who were not institutionalized. I am just suggesting a rubric. Obviously anybody doing this work will probably come up with more categories.

Group number two are those presently incompetent but those who are expected reasonably soon to be incompetent. A person with Alzheimer's is the paradigm here where one begins to think along the lines of the Maryland group, can we get some advance direction from this person.

The third group are those who are previously competent and there one might distinguish between those who are capable of assenting now or withholding assent where it makes sense to talk about informing them of the research and so forth and they can say no even though their surrogate has said yes versus those who are not capable of giving any consent or assent at all. They cannot tell you to stop or to start, or they do not want it.

And within each of these groups then there are those that gave you directions before and those who did not give you directions before.

Finally there is the group of the never competent, the mentally retarded who are never able to give consent. Now there too there may be those who can assent and those who cannot assent. So these are just an example.

I mean, I need an analytic framework and then within

that, Jim, it would seem to me there it would be useful to take these documents from Penn or Maryland, or wherever and have someone plug in --

PROF. CHARO: The proposed rule.

PROF. CAPRON: -- proposal. In other words, the Maryland group suggests we deal with it this way. The Penn group says this way. Somebody else says this way. And we could see what the alternatives are so we can begin to say what would we craft out of all of this. Okay. But this is not work we can do sitting around here around the table until the preparatory work has been done.

DR. CHILDRESS: Okay. Here is what I have heard so far -- does anyone want to add anything -- and see if we have a consensus about -- I would not say this direction, but these directions.

One thing we want to know is, in more detail, whether in written or oral form, the problem -- people like Charles McCarthy and others, why the initial proposals from the national commission and DHEW were not implemented. What kinds of factors were at work? What has changed since then?

Second, we are interested in thinking conceptually in terms of developing an analytical framework about implications of different models for whether we go on -- in an effort to do some research in this area or work with -- if not a prohibition at least a strong presumption against research with cognitively impaired subjects.

We want in an analytical framework to deal with the different kinds of categories that could be used whether we think about categories of research or categories of risk, or categories of competence

or incompetence, or capacity or incapacity. And we would like to see those dealt with in relation to the drafts of policy and regulation that have been proposed by different groups. And then finally we would like to hear from both researchers and patients/families about experiences in this particular area or arguments for or against research.

Have I -- is there a consensus that those are directions we ought to take? And, if possible, have some of this ready for the next subcommittee meeting. I mean, I have not heard how the next NBAC meeting will be structured and whether there will be a subcommittee meeting as part of that but I am assuming given the time frame that we are talking about a subcommittee meeting after the March one before we could have some of these things put in manageable form for us.

Is that direction --

PROF. CAPRON: The next one is only two weeks away.

DR. CHILDRESS: That is right. So that is why I am suggesting it is impossible.

DR. SCOTT-JONES: I have a quick question about --

DR. CHILDRESS: Sure.

DR. SCOTT-JAMES: The first item that you mentioned was reviewing why the regulations -- the proposed regulations were never accepted.

DR. CHILDRESS: Make sure everyone has a copy of those and to talk about why they failed with input from people who were involved in the discussion.

DR. SCOTT-JAMES: Okay. I was just wondering is there more to it than what we have already read? I am just trying to wonder

what value added we would get from what we have already read about that. I believe we need to talk more about it.

DR. CHILDRESS: I would like to talk more about that point but Alex is -- I would concur with you that I think we have heard from Levine, Bonnie and others in a way that I think we --

PROF. CAPRON: I originally just said have people received the regulation. I did not know -- have you read the regulations?

DR. SCOTT-JAMES: Not the regulations themselves. So I was just proposing that as a change to that first one. Maybe we need to look at the regulations and given what we have heard about why they were not acceptable, would we agree? Is there something more to it? It seems like step one is a repeat of what we have already done.

PROF. CAPRON: I would agree with Diane and suggest that in this analytic process that we are talking about, whoever was doing that would plug the regulations in, the individual provisions of the regulations, into this analytic description along with the Maryland and the Penn, and other things and say that was the way it was suggested there.

DR. CHILDRESS: Okay.

PROF. CAPRON: But there might be some value as we get to talking about it and get to our own point of saying we are ready to go with X, Y or Z to be reminded by people who lived through the comments on those regulations what problems and that is where I thought of someone like McCarthy.

DR. SCOTT-JONES: Then I have one more comment. It seems that our discussion this morning so far has not only addressed

the cognitively impaired but some much larger issues that apply to the cognitively impaired but apply more generally to the protection of people who participate in research.

And to give you just two examples that I think are very important and that we should comment on at some point, and that is what Alta mentioned about at what level should a body function? Should there be an IRB or a similar group at a level removed from the local level? I think that is a big issue that we really need to talk about at some point. Is there value in it and why would we leave the local model that most people right now seem to at least value.

And then the other issue is the one that Eric mentioned and that is the intertwining of regulation and education in controlling the behavior of people who are researchers. I think we really need to talk more about that and maybe have some sort of statement that comes from the commission on that issue.

DR. CHILDRESS: Okay. Other points? If people can -- have we said enough about that then to work out for next time?

If you could delay a break that was scheduled for about seven or eight minutes ago I would like to before we take the break get Charles McCarthy who has to go back to -- I mean, sorry, Charles McKay. Sorry, Charles. We have been talking about Charles McCarthy for so long that I have forgotten to whom we are returning now.

But I would like to have Charles McKay before he has to go back to a meeting at NIH to talk about the study that he is conducting and everyone should have received a copy of the first three instruments being used I put at your desk this morning.

So if you would join us at the table, Charles.

DR. McKAY: I did not have some materials.

DR. CHILDRESS: Okay.

DR. McKAY: There are some materials that describe precisely where we are.

DR. CHILDRESS: Welcome.

DR. McKAY: Thank you. I was present at the first commission meeting and presented you with a little bit of background on the institutional review board study and some information I had developed on the history of IRBs. I am pleased to be here to tell you what progress we have actually been making. That meeting was back in December.

As you can see from the little status report we have gone out as per scheduled with the first there questionnaires to IRB chairs, institution officials, and IRB administrators, and our response rates with the initial mailing, we have not done follow-up contact, have been quite encouraging. That is they are already over 70 percent. Correlating all of those across the board, however, we do not have yet a -- what I would consider important response rate that touches those representatives from all institutions. So that is our major focus at the moment.

The third focus is something I will comment on briefly this morning and I promise to make available to you within a matter of a week or two the actual questionnaires that will be sent out to IRB members and investigators. I contacted the contractor on Friday and they did not have a good clean copy of the latest and it is not back from the printers and they are still tinkering with wording, and I thought it

easier to wait. I will just tell you how those may differ from the questionnaires you did receive.

Overall we are studying, just to remind you, the institutional environment, including resources that are available. We are looking at questions of process and procedures that IRBs employ at several levels, including such mechanisms as subcommittees, primary reviewers, the way IRBs handle the paper flow, the way they divide tasks and looking at exempt, expedited, completeness of materials, what preliminary work they do with investigators to make the actual protocol presented to the IRB as complete as possible because we want to develop what looks like sound and good practices and have that information circulated.

We are also looking at more substantive process questions of how they rank order their time and the priority, that is what actually does happen. Do they spend all the time editing consent forms? Or do, in fact, they wrestle with risk-benefit and justification issues? And how satisfied are the chair and the administrator, and we will see later in the next set of surveys members and investigators with that process. Does it have a good outcome? How are they performing? And then we are looking at some demographic information about all of these groups, of course, but also some throughput and output information.

We have pretty reliable information on the way the system is now working and it is important to remember that IRB work loads have tripled since the national commission study in 1974. At the same time NIH success and funding rates have dropped precipitously from something in the neighborhood of 60 to 70 percent of applications to at

some places less than 10. And major institutions, stellar institutions in the research field are lucky to be getting 20 percent to 25 percent success rate.

We have seen that the number of applications then going to other sources of funding -- and there is no way for us unfortunately to track this. We tried in a pilot study with seven major institutions and it was simply impossible. They do not have records to allow us to know of those that get funded from other sources how many were originally turned down by NIH versus those that were submitted to NIH again. So we just forsook trying to know that at this point. That is a specialized study and would drain our resources. At any rate that gives you some idea of what we are looking at in terms of the work load issues.

Then we are looking at outcome. The outcome not only in terms of asking specifically about subject complaints, injuries, problems encountered, noncompliance of investigators, suspension of protocols because of noncompliance, but we are also looking at outcome measures as to what they have observed in terms of changes in investigator behavior or changes in protection of subjects as a result of these processes that we impose on them. And outcome in terms of what goes on educationally within the institution to ensure better compliance, greater awareness, greater appreciation of subject rights and safeguards.

We will carry those out across investigators and IRB members. The change with the PI surveys, principal investigator surveys, that I think are major interest, they will address specific protocol issues.

As I pointed out in the material distributed originally at that phase a subset of institutions in the general survey, the first three phases of which we have done, a subset of those will have protocols selected and divided equally between high risk, low risk research, behavioral research in biomedical institutions so that we at least have some assurance that we are not looking at only part of the picture. And we will see by a complicated algorithm four protocols that ought to have been implemented, indeed even completed by the time of this survey.

We will approach those investigators asking them to tell us about the status, the funding source, so that will enable us to get some idea of where the money is coming from. What sort of subjects, especially those in the long list of vulnerable categories, women, pregnant women, children, minorities, those who are ill chronically, acutely, those who have mental illness, those who may be economically and educationally disadvantaged and disenfranchised, the whole range so that they can identify where the subjects were in their protocol.

This will not give us a huge number of classes of subjects or protocols. This will only turn out to be about 1,100 to 1,200 investigators. If we get the response rate we hope for it will be between 900 and 1,000 responses.

But we think with the random sampling and the stratification we have used we can draw some reliable conclusions that will suggest room for future studies. Some groundwork will be done and something can move from there.

We will ask these investigators too about whether the studies require hospitalization, whether there is payment for

participation, the duration of specific parts and overall what is the period of follow-up, longitudinal if these are clinical studies. Do you check back periodically over time to see how the subjects are faring? We are going to ask them about their research methodologies as well.

Then we will ask the principal investigators what their own estimates are of risk-benefit, the consent procedures, whether they agreed with the IRB findings or not, how much concordance there was.

Now there is obviously a lot of room for soft information there because these will be things recalled after time. We are aware of that but this method was selected as one that would get us some information across the board. Obviously if you could focus in on a few select institutions you could sharpen this considerably but we wanted a broad look at the IRB.

And we will ask whether sponsors reflected similar concerns to the IRB. Then we will ask investigators about their perception of the whole IRB process, how thorough is it, how timely, what's the effect on the research, is it something that they find as in the initial survey of the national commission some 20 plus years ago, that in spite of finding this an unbearable and intolerable obstacle investigators grudgingly admitted that their protocols were improved as a result of the process. I expect we will find something like that.

With respect to members, and then I will draw this to a conclusion, we are going to ask about their experience as investigators, as IRB members, what orientation they have had, how their service on the IRB is assessed by them, what they feel of the workload, what they see of various -- how the procedures that I have described before,

prereview, assigned review, primary, secondary review, subcommittees, and so forth, how they handle these things. How they might affect their workload and effectiveness.

We will ask them to assess the performance of the IRB and we have some questions in there which will allow them opportunity to express concordance or not with IRB findings and how often that occurs.

Of the members, we will purposefully always select the noninstitutional member of the IRB. Of the others we will make efforts always to have representatives of various disciplines on there and of gender, et cetera. But we cannot guarantee that because the algorithm that we are using for this is a little harder to control on such a large scale. But it will always include the noninstitutional member because we feel that is a critical variable here.

We will ask them whether they spend too much time on the wrong things and enough time on the right things, and how they assess their role and what their estimate of the needs of the IRB. That is a common thread throughout. Do they need more staff or resources? How could we facilitate the process?

The results will be cross tabulated in a very complex matrix of variables where we will look at all of these diverse sources including document extraction and independent protocol review by expert committees, some 215 separate variables will be looked at and the sources of some of these will obviously overlap. So we should have a pretty complete picture.

Then of course the question is when? I have set a

deadline of March which the contractor tells me is not realistic. We are fighting that battle at the moment. There are some reasonable bases for delay and some that are unacceptable. But we are moving as rapidly as we can and what encourages us is the enormous degree of cooperation we are finding from institutions across the board at all the levels we have so far touched.

In fact we get phone calls frequently from Dr. Wendy Baldwin, deputy director of extramural programs down through the contractor, from institutional officials, IRB chairs saying we want to be part of that particular subsample. We remind them that is good news but it is going to be perfectly random and we cannot guarantee that they will get a place and that will not even give them priority in selection. But at least there will be something there for them.

I am happy to answer questions, Jim. I once again want to thank all of you for your interest in the study and for asking me to speak this morning.

DR. CHILDRESS: Thank you very much. That was very helpful. Let me pursue the timing question again.

Under your revision of the realistic time table you would hope to have all the surveys in now by, including the two instruments that have not yet been circulated, by when? Late April, early May?

DR. McKAY: I would say we are going to have to fish or cut bait on those. We are just going to have to maybe accept that we will not get as good a response rate as we would like by going back two or three times and simply cut off. So I think we will do an initial and a follow up. We would like to pursue it. There may be opportunity to

pursue it but that would have to be a separate contract and a separate funding. We simply cannot go on under this study any longer.

DR. CHILDRESS: And then once you complete -- you have the surveys back how long do you anticipate it will take you to analyze the data?

DR. McKAY: Well, some data entry has already been accomplished and I pressed the contractor to see what we could come up with. But as I discussed with you most of this falls into a largely demographic area, the very simplest of entry, and so it would have been really not very meaningful to go over where degrees are, and gender, et cetera, at this point.

DR. CHILDRESS: Right.

DR. McKAY: The analysis is probably going to take a little bit longer. I expect we should have key questions by June. I think this group could help enormously if they exerted pressure on me to exert pressure on the contractor to target specific issues. We are asking about things with vulnerable subjects, for example, if that is important to you. We are asking about various kinds of IRB procedures. We are targeting areas.

And I think some of those when we get the next return or response from institutions, those are not questions that are specific to members or investigators, we can learn from IRB staff and chair and institutional officials about some of those areas, about revising operations and procedures, and resources, for example.

DR. CHILDRESS: Good. Thank you.

Alex?

PROF. CAPRON: I asked that we have some updating on this and I am glad to have the questionnaires, Charles. I had in mind that we would receive a copy of the protocol, the study design, and you recited a number of items of it as you go along. I am just not quick enough to keep up with you so it would be useful to have that so I would have a better sense of --

DR. McKAY: Absolutely. I apologize for that. I will make it available.

DR. CHILDRESS: Thank you.

PROF. CAPRON: We had plenty to read.

From your knowledge of that already is there anything in your design that will yield responses on the IRB's sense of -- the extent to which the justice criterion is being examined by the -- just selection, fair selection of subjects for research? It is one of the long standing issues in research that the question has always been can they do that, do they do that. I did not see it listed in the list of considerations where they were being asked. This is the questionnaire to the chair and it is Section C on institutional review board operations on page CH20. Protocols reviewed by the IRB present an array of deficiencies and then there are four categories given, consent form, consent process, risk-benefit, and scientific design.

Under scientific design it says, "Numbers of subjects and inclusion criteria may make results equivocal or invalid." That is the scientific aspect. But I did not see the justice aspect, the fairness aspect teased out here. Is it somewhere else? Because obviously I do not know this document well.

DR. McKAY: No. It is -- I think indirectly approached there is a couple of areas. One, it is part of the member and investigator survey.

PROF. CAPRON: Oh, it is?

DR. McKAY: It is. That will not give us as full a picture as I think you are asking for. Secondly, we are asking all the categories about the difficulties and advantages and the process for determining whether inclusion of women and minorities is working. We feel that that is a new policy and we have not a chance to evaluate it. So indirectly we are getting at some of that.

But we made a cut in the questions. I should say cuts were made for us because at each stage we interacted with quite a large number of groups and unfortunately that was just not sufficient priority. But I think it is something we will try to get at indirectly. It had been in there as a featured item and it just -- because of the length we were told you will not get cooperation from our institution --

PROF. CAPRON: Yes, I get the picture. Yes. Now you heard a lot of discussion here this morning on the question of whether IRBs do a good job on assessing risk-benefit ratio and the way the design affects them. And we had statements from the Penn group that sort of suggested, gee, they ought to attend to that and then other people were saying not only do they attend to it but it is part of the present regulations they have to attend to it. And then Diane commented, well, some IRBs find that they do not have the expertise to do it.

Will that question you think be in a fairly detailed and nuanced way answered by this study? Will you be able to give a good

picture on that one obviously crucial question.

DR. McKAY: Yes, I think we will get a very good picture. We are not only triangulating. We are sort of coming at it from an independent point of view, too. We will get IRBs, investigators, and then we will have our independent panel looking at the risk-benefit. So we will be asking overall IRB chairs, administrators, and members how much time they spend on that, what priority they associate with it, and how much material comes in relevant to answering questions in that area.

We will be asking for the principal investigators how much thought they have given to it, how their thought concordat with the IRB on that. Did they gain insight into risk-benefit and the procedural safeguards that could be put in place apart from consent as a result of the IRB review? And we will be looking at a subset of those protocols blindly with a panel of experts to identify were there points missed, what would be the gold standard of looking at these protocols, are there risks and benefits that were overlooked by the IRBs and the investigators in the course of this. So I think we will get pretty solid answers.

PROF. CAPRON: Will your independent panel have any way of knowing how the IRB deliberated on a particular protocol? In other words, if it looks at it and says, "Boy, there was a risk here. I am surprised this protocol got through with this kind of a risk here." Will they have any way of knowing whether the IRB very carefully grappled with that as a risk and comes to a different conclusions, reasonable minds may differ, or was it just blind to it or it was ten times as bad in the first version but they got it down to this level? I mean, will they have any way of knowing that?

DR. McKAY: They will have some idea of that because they will through the process of document extraction be able to see the minutes regarding those protocols. That is it will sort of be we will follow these protocols through the review system.

PROF. CAPRON: Okay.

DR. McKAY: The expert panel will not make any comment on what the IRB has done. Those will just sort of be juxtaposed because we do not want to put people in the uncomfortable position of trying to judge in retrospect what people may have judged in the course of a rushed meeting with all kinds of other pressures.

PROF. CAPRON: Yes. Well, of course, the question --

DR. McKAY: But the world can see.

PROF. CAPRON: The question about the rushed meetings is the very issue at hand. Do the constraints prevent -- I had two more questions. They are both very small. One of them is just simply understanding this thing that you passed out to us. Where you say that there will be at 300 IRBs a sample of four investigators sent questionnaires for a total of 1,176. Now I just do not understand what happened to those 24 people who I would have expected to exist if you went and asked 300 times four. I just -- it is just --

DR. McKAY: It beats me.

PROF. CAPRON: Okay.

DR. McKAY: Our statistician handed me the numbers and after I had gotten a lot of grief questioning their methodology because of my ignorance of some of it I just said, "That is close enough."

PROF. CAPRON: Right.

DR. McKAY: For government work.

PROF. CAPRON: Now speaking of close enough and so forth, one of the concerns we have with our budget is to the extent to which we could ever, assuming that we exist beyond October, engage in any empirical work ourselves. I wanted to get a sense from you what has been the total budget for this study because it was announced a few years ago and it has, I gather, just sort of got underway in terms of the questionnaires now. But I am sure there have been designs in all this process. What was the total budget for your study?

DR. McKAY: The original budget for the two year period was $972,000.

PROF. CAPRON: And that is the external costs, not your time and other people, whatever.

DR. McKAY: Right. And -- well, it does include time for the consultants that work with the contractor.

PROF. CAPRON: Right. But not -- not your --

DR. McKAY: Not NIH time.

PROF. CAPRON: Not NIH time.

DR. McKAY: As we encountered a number of delays we have had to increase the budget another $500,000. So it is just under a million-and-a-half dollars.

PROF. CAPRON: Okay. Thank you.

DR. CHILDRESS: Any other questions?

Well, I guess on the timing issue we would love to have a thorough analysis as soon as possible.

DR. McKAY: I agree.

PROF. CAPRON: Charles, though, raised for us a question which is could we identify for the analysts those questions that we would like to have analysis of first. I thought it was a very generous offer.

DR. CHILDRESS: I think that is where we need the protocol in particular, I guess, to --

PROF. CAPRON: Yes.

DR. McKAY: That, in part, but briefly let me state Alex has mentioned risk-benefit and we could very well target that. Some earlier discussion talked about what is done educationally by way of resources provided to investigators in orientation, training, materials, models, forms, handbooks, consultation with IRB members and staff. If, for example, you wanted a more thorough picture of what are the best practices out there, what prevails in terms of how much IRBs devote to this part of the process, we could get that.

I think questions of how much time it takes for protocols to go through are of less interest to you, though. They are of more interest to some other groups. If it takes someone six months and several iterations to go through there may be problems there. But that is a piece of information that we would want to analyze for you. But those others are potential targets it seems to me.

And Alex has mentioned the justice. As I said, unfortunately, we will have to approximate that by some surrogate measures but at least we can get a focus on how it is being thought of, what additional measures of safeguard, procedural or otherwise are involved, and maybe some information, for example, the number of

complaints, injuries, harm, and things of this sort can be focused on. I think we can get that information.

So if you -- I will supply you with all of that and so if you can get back to me with particular areas of priority I will try to get even preliminary information that is even before we have our final round up of response. We could do something at a partial level because I think once we get passed the 60-65 percent across institutions results can be pretty meaningful and relied on. But I am a little afraid with 52 percent and different people answering with different degrees of intensity. It is not going to be clear enough for your direction.

DR. CHILDRESS: Okay. Wait just a moment if you would like. There may be some other questions from a couple of others. I would like briefly to report on Anna Miller's study that is now being developed. Some of you met her when she was here at the last meeting. She is a project leader for DHHS, Office of Inspector General, Office of Evaluation and Inspections, and developing a study of IRBs.

I have talked with her twice this past week about the study. The second time following a meeting that she and her group had on Friday. They are still designing the study and they would like to have our input regarding timing -- they would like it soon, preferably by August if possible -- the direction of the study and the methodology. So given what we have already heard presented and the instruments you have let me say a word about this projected study.

First, I have mentioned in terms of timing they would like to get the results to us in August. I wonder whether that would be a sufficient time to be helpful to us. Second, the direction of the study,

the study will focus on hospital IRBs and will be specifically concerned with the challenges hospital IRBs face in their efforts to effectively ensure human subject protection in the research they oversee.

The study will consider several challenges in a changing environment of research. First changes in the health care market. For example, hospital mergers and hospital care. What kinds of challenges emerge from these changes? Second, the challenges emerging from increases in private commercial funding of research. Third, the challenges emerging from shifts in the nature of the research. For example, genetics research or new technologies, or newly defined disease, diseases such as AIDS. And, fourth, the challenges emerging from increases in multisite trials.

The study will ask as it is currently being designed, and there will not be a final decision about the design for a couple of weeks, which of these changes present the most significant challenges to IRBs effective functioning. What strategies have IRBs designed to meet these challenges? And what implications do these challenges have for federal efforts to protect human subjects?

Now one question she raised for the Human Subjects Subcommittee is are these the most important challenges to highlight? Are there others that should be added?

Third, timing and direction, we have questions about methodology. The group had considered a broad based IRB survey but decided against it for two reasons. One is what you have already heard today, Charles McKay's IRB study. Second, it would take too long to conduct and thus the results might not be available to meet our needs

given our time pressures.

The preliminary proposal of method is that it would consist primarily of interviews. A number of IRB chairs and administrators would provide the core. The group would be especially interested in experienced chairs and administrators since they would have had a chance to observe the changes over time and the challenges that have emerged. A few IRBs in more depth, elites and experts, that is very knowledgeable people who have followed this discussion over time, commercial sponsors, agents for contract research organizations, key people at NIH and FDA, and perhaps even utilizing the IRB chat group in some way.

Another question is what kinds of suggestions might we offer regarding the method that is being considered.

Any responses at this point in light of what you have heard about Charles McKay's study?

PROF. CAPRON: The in-depth examination would be conducted by who? I was not clear if you were saying they were going to turn to outsiders who were involved in the IRB process at other institutions that were expert in the IRB process or all --

DR. CHILDRESS: The interviews would involve -- would be directed at all of those groups. There would be interviews conducted. This would not be a survey but rather interviews.

PROF. CAPRON: I understand interviews would be conducted. Who was -- I mean, it -- for the overall interviews, maybe I misunderstood part of the design, but I thought there were going to be an interviews at a number of institutions. But I thought you went on and

at one point said something about an in-depth examination at a few institutions.

DR. CHILDRESS: That is my impression of what she said, right.

PROF. CAPRON: Well, I would be very interested because of a recommendation that the President's Commission made for a general methodology of using a peer process. We thought there was -- since we did not think there was enough known about IRBs and that this was a chronic condition for the federal government not to know what was going on in IRBs except on paper, that a process of site visits of IRBs by teams assembled from people who were on IRBs at other places, the same way is true when an institution is applying for a center grant and gets a site visit or the like from peers. It would be a good idea.

And I would be interested if it were feasible within their design not only to use people from the Inspector General's office to conduct the interviews but that at a few selected institutions they would try using the site visit method. We used it. We pilot tested it. It seemed to work and then the idea did not go anywhere.

DR. CHILDRESS: Okay. Charles?

DR. McKAY: Part of our original design did include site visits but given the length of time and the need to harbor resources we discontinued that plan. But we think it is a very good one and I would sort of second Alex's recommendation that people working for some period of time in the IRB community be involved in those site visit interviews. It is essential.

It has been my experience that the type of interviewing

that is done by federal investigative bodies is very incisive but they do not have the prospective that comes from working within that system and I think it would also make the responses more productive for them if there were colleagues of the people they were interviewing involved.

DR. CHILDRESS: Any other suggestions regarding method or the challenges that have been identified?

(No response.)

DR. CHILDRESS: We will come back at the end of the day in light of these two particular studies and see whether there is something else you want to do now or think about later for further study of IRBs and the whole process surrounding them.

But anything else you would like me to pass on to Anna Miller?

(No response.)

DR. CHILDRESS: Because they would welcome our input as they are designing this study. Well, if something crosses your mind before the end of the day.

Let's take a quick five to seven minute break since we are obviously already behind schedule.

[A break was taken from 10:46 a.m. until 11:04 a.m.]

DR. CHILDRESS: Well, we will get started even though some of our members have been detained by those who are following media interested in sheep cloning and since the subcommittee has taken a position on this we have designated a few members who would be willing to go talk to the television crews about that topic.

We want to turn our attention now to a discussion of the

report of the committee looking at the Tuskegee Syphilis experiments, turning in particular to look at issues of legacy and what might be done in response to an experiment that continues to raise a lot of questions. An HBO movie was telecast Saturday night, for example, "Ms. Evers' Boys," deals with that topic. And it is one that remains very important particularly in the views of African Americans about research as well as some other issues like organ donation and the like.

I have asked Professor Rhetaugh Dumas to kick off the discussion for us.

DISCUSSION OF THE REPORT OF THE TUSKEGEE SYPHILIS STUDY LEGACY COMMITTEE

DR. DUMAS: Okay. Let me just briefly review the points that I think are salient points in the report of this committee.

This is a group that was formed last year at a meeting at Tuskegee Institute and they are a forum to keep alive the legacy of the syphilis studies at Tuskegee and to try to counter the negative impact of that legacy which they believe has come to stand as a metaphor for racism in medicine and health care and ethical misconduct in human research.

They did point out a number of implications for the delivery of health care, for organ donations, and for the general suspicion that is often referred to in African American communities of the health care enterprise, and they are hoping that by their recommendations they can lead an effort that would provide public education and opportunities for scientists to understand more about the impact of a suspicion in the Black community that is aroused by such

incidents as the Tuskegee Syphilis study.

Specifically they are recommending that the President of the United States makes an apology for this event, that he apologize for the suffering or whatever the consequences has been for the people who were involved, and that that apology be made at a public -- at a meeting of this -- of the biomedical -- the -- our committee, the Biomedical and Ethics Advisory Committee.

And, also, they are recommending some other remedies to establish a museum and a way of preserving records, a number of records that they feel are in jeopardy, and have a center at Tuskegee for the study of issues that would be related to ethical conduct in research.

Then there are two or three other initiatives that they are recommending be undertaken by the government, a program similar to an office to be established similar to the one that is currently existing on women's health.

Now when I thought about this I thought, you know, their recommendations sounded good to me and I wondered whether or not this committee would be amenable to endorsing the recommendations. But then on second thought I thought that the Tuskegee Syphilis study is of sufficient import for the work that we are undertaking as a commission that maybe we ought to give more serious attention to a more thorough analysis of the ethical issues that were involved so that we could have some lessons that we can pass on from this event and other similar events like the radiation experiments.

So I wonder, also, whether or not it would be preemptive, not preemptive but -- what is the word that I want? It would be too early

to make a decision about endorsement prior to understanding the nature of the ethical issues and get some ideas about what measures might be recommended to ensure that these kinds of problems could be forestalled in the future.

So I am asking you to think about, one, the implications of the Tuskegee Syphilis study for the work of the commission in general and whether there is sufficient import there to warrant a more detailed discussion or at least a more detailed written analysis of the various perspectives on this issue. And then, secondly, whether or not the commission is amenable to getting involved in recommending or supporting remedies.

I think that those to me are the key issues that are raised in my mind when I read the report.

DR. CHILDRESS: Thank you very much. It might be possible as we think about this to consider working on two levels.

DR. DUMAS: Mm-hum.

DR. CHILDRESS: One might well be, if the subcommittee wishes, to recommend to the administration or to NBAC to recommend to the administration at least an apology but that is the sort of thing that is currently under discussion. For example, the head of CDC last week said in an interview that the government is considering that and they would anticipate an apology from the President but they do not what time that would happen. So it is something currently being discussed and one question would be whether it would be useful or not if the subcommittee wishes to endorse this direction to consider this without in any way undermining support for drawing substantive procedural

lessons from the experiment, that is to say what can we learn about prevention, what can we learn -- what should we do about remedies?

So we might consider at least both levels. What kind of immediate response and another that would involve us incorporating issues as we continue to think about the whole area.

What other thoughts do we have?

Arturo?

DR. BRITO: Well, I definitely think it is important to go along with this recommendation for the public apology, et cetera, and also maybe concurrently to even have a meeting in Tuskegee at some point in the future or maybe during that public apology.

I think it is a great example of how -- we are going to get to the subject later about vulnerable populations, et cetera. We are not talking about persons that were cognitively impaired and yet they were vulnerable enough to be included and be victims of this research. So I definitely feel that we need to look at that and see what it was that made the scientists in the research believe that they were doing the right thing and so that those can be avoided in the future with our future experimentation.

I forgot. There was another point I was going to make but I will come back to it in a second.

DR. CHILDRESS: Okay. Other --

DR. DUMAS: What about the other recommendations? One recommendation is the apology. And I gather that that is a more pressing area for decision at this particular time, whether or not this group would endorse that recommendation for the public apology. But

then there is the issue of whether or not the meeting would be held and the apology would be made at the time of our meeting, and that is something that I guess this subgroup would have to recommend to the broader body, the committee.

DR. BRITO: The only question I have on that is how does it fit in with our time line that right now we are concentrating on the cognitively impaired and even though there are a lot of similarities because of the issue of vulnerability, so where would we want to put that in terms of time? But I think at some point we definitely need to address it and agree to those recommendations.

I think concurrently having it -- I think one of our jobs as a commission is to raise public awareness of some of the issues and that definitely they could be advantageous to the public if we had it concurrently with one of our meetings. So, you know --

DR. CHILDRESS: Well, perhaps I was hasty in talking about two levels, perhaps there are three.

DR. DUMAS: Yes.

DR. CHILDRESS: One might well be the apology which is the most significant and symbolic act that the Legacy Committee is focusing on. But then closely related to but distinguishable from that would be the other series of responses, preservation of documents, setting up of a center, and so forth, and that is something that we might well commend for attention as distinguished from recommending.

DR. DUMAS: Recommending, yes.

DR. CHILDRESS: And then there is a third level which I think we are all very concerned about, too, and that is the lessons and

that would be an important part of what we do over time, I think.

DR. DUMAS: Well, it would also be very nice if this public apology was going to be made at a meeting of NBAC that we would have some clear notion about the various issues that we would want to highlight. So all of those things kind of link for me.

DR. CHILDRESS: Right. Okay.

DR. SCOTT-JONES: I would like to add something.

DR. CHILDRESS: Please.

DR. SCOTT-JONES: I think that the suggestions that Arturo has made are great ones. I think the symbolism involved in our having a meeting there would be really great and I do not know if it is appropriate for NBAC to send a letter to the persons working on this commission saying that we will do these things that we are discussing. I think we could point out that many of the issues that we are discussing now are relevant to the activities that happened during the Tuskegee Syphilis experiment.

And some of the new ways of thinking about research ethics such as the community perspectives because certainly persons other than the individuals in Tuskegee were harmed by individuals' participation in Tuskegee. So I think some of the ideas that we are going to talk about related to community are ones that are really relevant there and we could point these things out in a letter to the persons who are working on this.

DR. BRITO: I think the real importance of this -- again you touched on this a little bit, Rhetaugh -- is to gain the trust of the African American community in medicine in this country because I know

from personal experience, speaking -- especially the grandmothers who are taking care of children, particularly HIV positive children, have expressed to me that they do not trust when we make medication changes that have been shown to be beneficial to the children and I have had one grandmother specifically tell me she is worried that what we are doing is experimenting.

This is coming from this legacy of Tuskegee and other such experimentation. So I think there is a world of mistrust and the medical community is often very critical of poor minority groups not being compliant with recommended management of certain diseases, et cetera. And a lot of that comes from just mistrust. So I think that is the real importance of raising this public awareness and making -- being part of this public apology to say we are ready to move forward.

In essence, what is happening is that minorities and -- I do not know if you agree with me on this -- the African American group in particular, the blood donations and tissue donations is a very low priority. And I wonder how much of that has to do with the trust of the medical community.

DR. CHILDRESS: Yes. Would you introduce yourself?

DR. SNYDER: I am Dick Snyder, Director of Science at CDC.

I just would like to make a few comments for clarification. First of all, though, I would like to say that I am very pleased that the subcommittee is addressing this topic. It is something that we in public health feel is very important and share the views that have already been expressed about the impact of the Tuskegee legacy on our ability to do

public health in this country.

When this meeting was held, and it was originally sponsored by CDC and the Office of Minority Health of the Department, although the committee itself is independent, the National Bioethics Advisory Commission had not been established.

So the idea really was to have a presidential apology coincide with the announcement of the naming of the members of the commission. That obviously did not happen. We continue to be in dialogue with the department and particularly with the White House now with regard to an apology and hope that we will be successful in that regard.

I believe one of the things that we feel is very important is that wherever the apology is done, although we think it would be nice if it were done in Tuskegee, but wherever it is done that the Tuskegee survivors be present and other people who were associated with it.

Insofar as the issues of what does one do to help make reparations for the harm that has been done, we have had some thoughts that we passed on. This -- one of the main things that we feel would be helpful in this regard is greater involvement of the community in research. More significant involvement in helping design and monitor the research and even translate it into the community. And, in fact, in the behavioral and social sciences area at CDC we have a lot of good examples where that has proven to be very helpful.

I think if the President were to make an apology one of the things he would really have to do is to make some general statements on what kind of things have been done since Tuskegee but

what things should be done in the future so that -- although I understand the need to study this issue very carefully and make appropriate recommendations -- some general statement, I think, from the President would be expected if an apology were forthcoming.

I hope those comments are useful.

DR. CHILDRESS: I think they are very helpful and thank you very much.

Any questions that you would like to raise?

Okay. Thank you.

All right.

DR. DUMAS: Well, it seems as if -- I -- from the discussion so far that we should endorse the recommendation for the public apology and commend the committee's recommendations of other efforts to --

DR. CHILDRESS: For consideration?

DR. DUMAS: For consideration. And then the third thing is how can we in the short time frame that would be required pull together something -- some information about what has been done, what kind of improvements have been done since this happened. That ought to be something that we should be able to do.

DR. CHILDRESS: Alex?

PROF. CAPRON: Again, I have to ask whether we were given a copy of the Tuskegee Syphilis study report.

DR. CHILDRESS: Does somebody --

PROF. CAPRON: Is it one of the things we were just given?

DR. CHILDRESS: He is not asking about the --

PROF. CAPRON: I am not talking about -- I am talking about --

DR. CHILDRESS: He is talking about the '73 report.

PROF. CAPRON: Exactly. I do not think so.

DR. CHILDRESS: No.

DR. DUMAS: No, we do not have that.

PROF. CAPRON: One of the ways that we could ensure we are not simply issuing platitudes would be to look at that report's recommendations and say how many of those have been implemented because as the gentleman from CDC said, I think for the President to make a statement on this, it would be natural for him to want to note those advances which have occurred. But we ought to also be attentive to those that have not occurred. And that panel made certain recommendations which have not been acted on and it would be appropriate for us to return to those and examine them. So I think we are going to need to have a copy of that report. It is not a long report.

DR. CHILDRESS: Right.

PROF. CAPRON: It is longer than this. I think it would also be useful to be brought up-to-date on what reparations were paid to the individuals and families.

DR. CHILDRESS: Right.

PROF. CAPRON: I do not -- what struck me was I did not see anywhere in this report any discussion of that.

DR. DUMAS: There is just a mention that the surviving families have had free medical care.

PROF. CAPRON: Well, more than that was gotten by their attorney whose name suddenly escapes me.

DR. SCOTT-JONES: At one of our previous meetings we were given the report.

PROF. CAPRON: Yes. Right.

DR. SCOTT-JONES: It was close to $3 million in 1995, right?

PROF. CAPRON: Right.

DR. CHILDRESS: But it was spread out.

PROF. CAPRON: What I am saying is that this report makes no mention of that.

DR. SCOTT-JONES: No, it dose not.

PROF. CAPRON: So it is sort of curious. I am sure that whoever is advising the President would say there is great value in having an apology. It is important to know that some compensation was already paid but that does not address the broader community issue of trust or distrust.

DR. CHILDRESS: Right.

PROF. CAPRON: Which an apology might go some way towards addressing.

DR. CHILDRESS: Right. And this is just one document that fits in a larger context of discussion at CDC and elsewhere about appropriate kind of response. But I quite agree with the points which have been made.

I guess one question is whether we would like to recommend -- given -- first of all, the desire that I have heard that we be

more specific given what has been done and what has not been done by reference, for example, to the '73 report, that one possibility would be for us to recommend to NBAC and that we endorse this in the way you have roughly suggested.

But that as part of that we have for the next meeting -- that is the NBAC meeting in March a couple of weeks from now -- the further information because we are not talking about a lot on the basis of the report. But something that could be useful but a lot of that has probably already been done by CDC and elsewhere, but at least for our recommendation if we choose to make one we could go in that direction.

What is your will?

PROF. CHARO: Jim?

DR. CHILDRESS: I am sorry. Alta?

PROF. CHARO: If I can make a friendly amendment to that suggestion. I have been fortunate that at my university is one of the co-chairs, Vanessa Gamble, who has been leading this effort. I urge that we invite her to come and address the commission as the person who has been involved very much in both the drafting of this and in working with HHS, CDC, et cetera, on this question because it does not seem to me a difficult recommendation to make that an apology is appropriate.

We have seen apologies used in a variety of other settings now with regard to radiation victims, victims of the Japanese internment, et cetera. And regardless of whether compensation was offered, the admission that this was a bad thing to do would not be a difficult thing to recommend since there is no lack of consensus on that point.

DR. CHILDRESS: Okay. So I think you are taking the

earlier discussion and you are now formulating it in terms of a bona fide motion.

PROF. CHARO: Sure, if you want to do it in that way.

DR. CHILDRESS: Yes.

PROF. CHARO: I would like to move that we recommend to the full commission that we endorse the request for an apology from the federal government to those people who were subjected to this. To the extent that it would be helpful in moving that forward I would suggest along with that motion that Vanessa Gamble be invited to present if she wishes.

DR. CHILDRESS: And that we examine the report and flush out this for the next --

PROF. CHARO: Indeed, she can be asked specifically to address that in her presentation.

PROF. CAPRON: Address?

PROF. CHARO: Address that clarification that you request in her presentation.

PROF. CAPRON: I do not disagree with what you are suggesting. I have the sense that given the noncontroversial nature of the recommendation that we probably do not need to have Professor Gamble come and explain it to us again. I mean, mostly it seems to me -- everything I can see that we have been told is it is more or less a matter of timing and how quickly among the things the President is prepared to do there is enough background presented by this committee and by the CDC process to come up with language and an appropriate statement. We ought to endorse that and urge that it happen.

PROF. CHARO: Right.

PROF. CAPRON: But I do not need any more convincing than --

PROF. CHARO: Right. I understand that completely. If we were able to get Vanessa Gamble here I think that she in her area of expertise which cover the history of medicine with special attention to race issues both from the point of view of patient populations and professionals. Is it a good position to talk about the broader significance of the Tuskegee experience and the notion of the apology here.

One of Professor Gamble's frequent points made that I have heard is that the -- to the extent that there is distrust in some communities, particularly some ethnic and racial communities in the United States about the research endeavor, that that distrust is not traceable to Tuskegee. It was not caused by Tuskegee.

That distrust predated Tuskegee because of a variety of other experiences and Tuskegee was an outgrowth of the kinds of things that have generated that distrust. It was not an isolated incident. That is the kind of point that does tend to get lost so that an apology seems to be part of the very isolated incident with an isolated response. And one of the values I see of bringing Vanessa Gamble here is that she can open this open up and talk about the larger problem of trust in research.

DR. CHILDRESS: And begin to deal with the kinds of lessons that --

DR. DUMAS: Yes. I think that is very important because I think that having the apology made and whatever the nature of the ceremony is not the endpoint of all of this. I think that we need to think

about cases like this in their broader context so that we can learn something from it and I would not want us to in any way give the impression that we think that the problem would be resolved by the President making an apology or even by the number of dollars that have been given to the families.

I think more importantly we would want to be able to tease out how these things have happened. What safeguards are needed in order to ensure that they will not continue to happen. And some intelligence on whether or not there are similar things occurring right now.

PROF. CAPRON: I agree with that and I think that if we are going to do that we ought to prepare to have some discussion with Dr. Gamble and other people who are involved --

DR. DUMAS: Involved in that discussion.

PROF. CAPRON: -- in some -- with some good preparation. I mean, if on the first anniversary of this commission, assuming that we are going to have future years of life, we were to meet in Tuskegee and devote an entire day or two to the issues of populations that are vulnerable for racial, ethnic and economic reasons instead of only for reasons of age or mental incapacity, and really have some in-depth examination of that.

The national commission had a whole process, including a conference, on minority concerns about research. I mean, they identified that as an important set of issues. It would be worthwhile looking at what was said then and how adequately it has been responded to. Again, as with the Tuskegee Syphilis Task Force report from '73, I

think we ought to look very carefully and say what things did they say that are still problems that need further attention.

So I would be in favor of doing this not just hearing from Dr. Gamble but from a wider array of witnesses on a well planned day or two in which these issues would be looked at in-depth with as much empirical information about what we know just the way we now have very excellent studies that show the differences in health care and health outcomes for minority populations which ought to be very high on the public agenda because they are a continuing shame for our country.

DR. CHILDRESS: But I think we hear several things. One in support for the action of the apology, a recommendation that some things be explored in more depth in terms of possible reparations, but especially importantly for our work an effort to think more systematically and empirically about the kinds of lessons that we could gain from this.

I would like to bring this to a close because we still have a lot to do before noon. But, Eric, any comments?

DR. CASSELL: I think I want to endorse what Alta just said and what you just said. The Tuskegee experiment was not done by people who were venal in that sense that we were talking about before. It was done by people who thought they were doing a good thing. That is what makes it so awful. When bad people do bad things that is not particularly interesting. It is when good people do bad things. The level of racism and disregard for people in other groups, both social and ethnic, was pervasive and it is still pervasive --

DR. DUMAS: It is.

DR. CASSELL: -- in the aspect of society. So the problem

that we are talking about, the problem of the protection of human subjects is, in part, a problem of the recognition of the need to protect. In that instance the need to protect was a nonperson sitting opposite and too many research subjects are still nonpersons. After all the patient -- remember we used to talk only -- it is only forty years ago that we spoke about the patient is a person, the patient is a person, that is the language you use when the patient is not a person. You do not need that language when the patient is a person. And so in that -- that is just a few years.

So the essence of this commission's work is directly relevant to the experiments and to the lesson that it teaches not about an isolated group or that it is an African American community but, in essence, that the relationship of persons who do research are the persons who are sitting opposite them, and I think we ought to mine it for all it is worth both for the people who suffered from it in more than one way as well as for the people who have not even yet been born.

PROF. CHARO: Jim, I am not trying to argue with Eric or with Alex because I do not disagree with what they have said but I would like to urge that having something done properly in some depth and getting back in the people who did do exactly the meeting that you are discussing, Alex, just this year at Tuskegee under the direction of people like Vanessa and others, I do not think that any of those preclude having Dr. Gamble showing up in March if there has been no action so far at the federal level in order to give more prominence to the commission's endorsement of the need for an apology if the commission goes in that direction because I think this is something that easily could get buried

and lost.

Although I agree with Eric about the origins of it I also think it is very important to never let the racial aspects of it get lost in the generalizability of some of the lessons because I think there is a very special, special risk that minorities have been running in the United States over the years of being the subject of this kind of disregard and we should not let that get buried in the fact that a lot of people have suffered the same problem.

DR. CHILDRESS: So if I hear your motion I would like to bring it to a close. It is to recommend an apology and to commend for attention the other aspects, and to invite Vanessa Gamble as part of our recommendation to NBAC at the March meeting, and then finally to develop in a way yet to be determined more systematic examination of the issue. Is that your motion? If you do not mind, I am putting words -- some words in your mouth.

PROF. CHARO: It sounds like your motion now but I will go for it.

DR. CHILDRESS: Is there a second?

DR. DUMAS: I second.

DR. CHILDRESS: Okay. Any further discussion?

DR. BRITO: The only thing is in terms of once again timing I would definitely like to see the report as Alex suggested before we have any speakers, Dr. Gamble, and I am assuming we can get that done before the March meeting.

DR. CHILDRESS: Yes.

DR. BRITO: That would be helpful.

DR. CHILDRESS: We would like to get that out immediately, yes.

DR. SCOTT-JONES: And could we also ask the rest of the commission members by E-mail or some way about sending a letter supporting the request for an apology since that may be more urgent than the other things?

PROF. CAPRON: Is our notice of the March meeting general enough to allow us to take it up at the March meeting?

DR. HYATT-KNORR: There is always room at the end of the Federal Register notice and other issues as they come up or as they emerge, or as they relate, and this certainly relates so I do not see a problem.

PROF. CAPRON: Perhaps, however, if this motion passes, Jim, you could send around a draft of what the motion that would be made at that meeting would be so that people who are not members of the subcommittee today could be well prepared for it.

DR. CHILDRESS: Okay. Ready to vote? All in favor of the motion indicate by saying aye.

(A chorus of ayes was heard.)

DR. CHILDRESS: Opposed? Abstentions? Okay.

DR. DUMAS: We usually communicate to the other subcommittee the kinds of things that we are doing and I think it would be important to send that report to the other subcommittee as well.

DR. CHILDRESS: Yes.

DR. DUMAS: So that they would be prepared for the March meeting.

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

In the short time before lunch we want to get started a discussion of the agency review, one of our mandated tasks.

I think, Bill, you are going to introduce that discussion today?

FEDERAL AGENCY REPORTS ON HUMAN SUBJECTS PROTECTIONS

(Dr. William Raub, Joel Mangel, J.D., and Ms. Emily Feinstein, NBAC Staff)

DR. RAUB: Thank you, Jim. I will ask Joel Mangel and Emily Feinstein to perhaps come to the table here.

We have a brief item of follow-up to your previous discussions. As you will recall Gary Ellis in the auspices of an interagency committee that he chairs anticipated the needs of the commission by requesting information from the several federal agencies that are covered by the Common Rule and some others as I understand it responded as well.

The staff performed some preliminary analysis that has been the subject of discussion by this group already and we neither propose to revisit those discussions unless you have particular issues but did want to capture some ideas with respect to the next steps.

I have asked Joel and Emily to distill the issues as they see them that would be the basis for the next phase of this study which would be a staff based inquiry with the other agencies.

In addition, we have been fortunate to negotiate the services of Dr. Bill Friedman, who is over here on the side, who is with

the Indian Health Service. Bill has extensive experience in both the principles and the underground practice with respect to human subjects protection in general and IRBs in particular and, therefore, will be a valuable asset to the staff group in leading that effort to bring the core of information together that I think the commission needs to make its next deliberative steps here.

Joel?

DR. MANGEL: Actually Emily will start off.

DR. FEINSTEIN: This is mostly a progress report on where we have come to since the last meeting. We have begun again to go back into the responses and to do an analysis in preparation for developing a final report and we have been hesitant to go ahead without a project director but we have decided that our initial approach of agency by agency is perhaps misguided. And in a re-review of the responses we feel that because they were more conclusionary and less substantive we wanted to undertake face-to-face interviews with the agency representatives in order to get the more detailed information we are looking for.

So with that aim in mind we have developed a list of generic questions that we can bring to each agency at each interview. They have been distributed to you. I do not know if you have read them. These generic questions were designed with the intention of --

DR. MANGEL: Has everybody gotten a copy?

DR. FEINSTEIN: It says, "First draft of February 24, 1997."

PROF. CHARO: Oh, that was from you. I did not know

who that was from.

DR. FEINSTEIN: "Questions for agency interviews."

PROF. CHARO: I did not know who that was from.

DR. FEINSTEIN: This is from us. This is a generic list of questions with the intention of going through the policies and procedures of the Common Rule step by step at each agency and we feel it will develop a broader and more continuous base of data that we can work with. And then in addition to that we can go over specific questions that we have that have come up in the agency responses.

For example, certain agencies claim that all the research they do is exempt from the Common Rule and that may be something we will want to discuss further.

We have been hesitate to schedule these meetings because we have had staffing issues but we feel that we can probably start moving right ahead now that we have Bill Friedman with us and we would be willing to begin as we have unless we have comments from the commissioners or from Bill as to how we can further refine our proposal.

Do you have anything to add to that?

PROF. CHARO: Is she asking for the comments now?

DR. CHILDRESS: Are you wanting comments now?

PROF. CHARO: Are you asking for comments now?

DR. FEINSTEIN: If you have. I mean, I am assuming at this point you have read the responses.

DR. MANGEL: Even the packages.

PROF. CHARO: We have read the responses, yes. But these handouts only came today, right?

DR. FEINSTEIN: Yes.

PROF. CHARO: So --

DR. SCOTT-JONES: May I just raise a point about procedure. In the future when we get documents like this could they be better labeled and could they be dated as well because the heading is "National Bioethics Advisory Commission," which is us, yet we have not input.

DR. CHILDRESS: That is a different one.

DR. SCOTT-JONES: This is not it? Oh. Okay.

DR. FEINSTEIN: It says, "First draft, February 24th."

DR. SCOTT-JONES: Oh, okay.

PROF. CHARO: Yes, this is our's.

DR. SCOTT-JONES: This is our's. Okay. All right. Let me find the right thing. Let me see what it looks like.

PROF. CAPRON: One page, two sides. "First draft."

DR. SCOTT-JONES: Thank you. Okay.

PROF. CAPRON: I wanted to understand the process a little. These are going to be sent in writing to them before you meet with them and you are going to get written responses and then go talk to them about their written responses? Or you are going to send them in writing and then go and talk responses orally?

DR. FEINSTEIN: Probably the latter. I envision that we will send the questions, that they will be prepared and know what we are bringing to the table, and that we will also request copies of any policies or relevant materials, educational materials, and we will have those before the interviews, and then we will go and speak. I am not

envisioning any more written correspondence before these interviews.

PROF. CAPRON: And you anticipate these will be with the individual or do you see a group of individuals in most places?

DR. FEINSTEIN: I am envisioning a group of individuals. There is an agency representative that has been designated to speak to us. But probably we are going to want to speak to more of them and to some people who have more day-to-day practical experience with the implications of the Common Rule and anyone else that the agency representative feels would bring something to the conversation. I mean, this is not an interrogation. We are trying to share data and, you know, learn as much as we can.

DR. CHILDRESS: And I have asked Alta and Alex both to look careful at what was received and to think about how we might move from here forward.

PROF. CHARO: Yes. I think Diane's point is well taken because it has been hard to figure out what is coming from whom. But now having seen this only for the last 45 seconds while you were talking I can tell you that we will be happy to send back comments after we have had a chance to review it properly. So that is number one.

Number two, already I can imagine that you might want to get some real basic information like how many protocols do they administer themselves? How many contracts do they have out that involve a contractor taking on this task? How many human subjects have been enrolled under those various protocols? How many adverse events have ever been reported? How many requests for compensation have ever been received? How have those all been resolved?

PROF. CAPRON: You are specifying some time period?

PROF. CHARO: There would have to be definitely a time period, yes. I had not even thought about that, but yes. In order to just get a handle on the magnitude of what is going on because the responses we got were so variable and varied in their ability to do this. And I suspect that that is going to take them a long time to do because most of them have no audit procedure that they have gone through with the exception, I think, of the CIA which clear did have an audit although we did not get a chance to see the report.

By the way can I put in a request that we get the Inspector General's report to which the CIA response refers?

And so that might be a great thing to get even before we get into the details of the procedures. It is just the magnitude of the activities as well as the classes of activities as you have already anticipated because some responses did focus on the fact that is more social science than biomedical.

DR. MANGEL: Yes. One of the things that came through very clearly from reading the responses is that we were going to have to be basic and so I agree with all of that.

PROF. CHARO: Okay.

DR. MANGEL: When you get a chance to look at the questions I think you will see that we really did at least think we were starting at a very, very basic level.

DR. DUMAS: I have just a suggestion for question number nine. In the other questions you ask them to explain what they do and in nine you just ask whether or not they monitor IRB activities. I

think it would be useful to know how they monitor or what mechanisms they have for monitoring.

PROF. CAPRON: We were also given a list in our places of the agencies that have responded to Executive Order 12975. And I do not see the Department of Housing and Urban Development on there but I recall that they had a response which is only a lead in to my -- I wanted to make sure that I had recalled that correctly. Their response was to say they sponsored no research. It was a one sentence response.

DR. FEINSTEIN: Yes.

PROF. CAPRON: That certainly was not once true of the department. And I wondered as a generic matter if it would be helpful to people to remind them of the definition of research so that you not go in and have a fairly fruitless interview with any of them. Obviously some of them may admit to doing some research but may not recognize all the things that qualifies as research, particularly social policy sorts of things. And just -- and so you are in agreement that that is --

DR. MANGEL: One suspects that Housing and Urban Development is not alone in the need to have that done.

PROF. CAPRON: But the --

DR. MANGEL: I agree.

PROF. CAPRON: Yes, I mean one of the issues that also came up was about the prison system because they have had a moratorium or prohibition on biomedical research for a long time. But when Professor Charo and I were talking about this last night. She raised the question of what happens to prisoners who happen to be enrolled in a biomedical experiment of some sort, they are getting a

research drug if they go into the prison.

I would suspect that the prison doctor becomes their doctor. They do not have an outside doctor coming in to treat them but I do not know that that is the case. But then does the department have any way or any responsibility vis-a-vis their continued participation if they are now prisoners but are on a research protocol or do they get knocked off of research protocols automatically. You cannot be on one if you are in the federal prison. That would be an interesting question to have answered.

There were also assertions in some of the publications that we got, not the regulations themselves, that for some departments, research that they conduct in-house they regard as not covered and the Science magazine with a brief description of some of our work -- or excuse me, of Senator Glenn's bill, I think, said something along that line that one of the things the bill would do would assure that in-house research was subject to these rules and not just research that is conducted outside.

That astonished me because, of course, the origins of all this were Surgeon General Stewart's policies which were built on the Clinical Center's own internal policy. So this began as something that was applied to government scientists doing work in-house. And I wanted to make sure that your questions teased out whether any of them interpret the Common Rule or their application of the Common Rule? Is that in there?

DR. MANGEL: Well, yes. I think that in a couple of --

PROF. CAPRON: The intent of --

DR. MANGEL: -- in a couple of the questions we tried to get them to explain some of the differences that their responses seem to lay out between intramural and extramural. Some of the responses indicated what you are saying. Some of the responses indicated perhaps a general misunderstanding of the different -- of similarity of the two, not the difference part of it.

PROF. CAPRON: And the final thing was one of the things that I had requested in talking with our chair last week, and that there was not time to prepare, would be some kind of a grid on which -- for the next go around you would identify for us where you think there are issues by letting us look at it graphically. I just find that for these complicated things we are trying to follow a whole bunch of regulations through a lot of departments to see where you found problem areas with notations of what those were but laid out on a number of pages by departments and agencies.

I had thought that perhaps you were doing this already because when you talked to us in January you mentioned that you found some of them more deficient and saw areas for follow-up. And I thought perhaps you had a working model of this sort. I gather you do not. But I would think in the future either you or the rest of the staff would prepare such a document for the commission.

PROF. CHARO: Yes. Again thanks very much for the list of questions. I have had a chance to scan them and they do cover a lot of things that I agree need to be explored. So it is wonderful to see a meeting of the minds because it is kind of a reality check on your own impressions.

I might want to add a couple of things, and forgive me if they are there and I just did not catch them because I was reading so quickly. When I went through the reports there are certain themes that emerged several times that might be worth some attention.

One, there seems to be continuing confusion and/or frustration regarding survey research and the meaning of survey research and when it requires review of what type, and it comes up in several agency reports. And it struck me as the kind of question that is a perfect segue into the discussion about where the interpretation of the Common Rule's regulations should be located within each agency and whether, as does not exist now, there ought to be a definitive office that interprets those regulations on behalf of all departments because currently the secretary at the top of each cabinet department has the final authority for the interpretation within that department.

So interpretations can vary across these departmental lines over the same language that has been adopted and common despite the efforts of the harmonization task force.

But with regard to surveys you see coming up over and over there is -- in some reports there is the request that there be consideration of a more realistic, practical, abbreviated set of procedures regarding surveys and yet if you look at the surveys that are being in many cases they are surveys that are already either exempt or eligible for expedited review.

So without further discussion with those agencies it is not clear whether this was caused by confusion or because the expedited review process itself is seen as being too cumbersome and in need of

further revision in the opinion of that agency.

And the distinction between evaluation of service delivery projects and survey research that, in fact, does trigger real review because it talks about sensitive topics that could put people at risk socially. For example, survey research or service delivery research pending that has to do with the reproductive area or with HIV status, to take two examples, is something that I think needs to be teased out a little bit more exactly what is being done, how it is being treated within the agencies, who made the interpretation to treat it that way, and whether there is some pattern and logic to this because I can only imagine that it is aggravating for people who are trying to do their jobs properly to never be sure if they are following the rules.

Second with regard to interpretation it has to do with the provision that permits in the transnational context, permits approval of research that meets equivalent sets of protections to the ones that we have in this country for reasons that the CIOMS group to which there has been some reference from time-to-time -- for reasons which the CIOMS group has spelled out.

Reasons of cultural difference, practical difference, the way in which you might have the same level of protection at the end by different sets of procedures. The WHO has somewhat different rules than we do for example. But which particular international organization sets of recommendations or which particular foreign country's legislative rules will be considered equivalent to our's is one that is still a kind of department by department or even IRB by IRB determination.

Again a better handle on the frequency with which that is

happening, when it is federally agency sponsored research, and the consistency of the interpretation of what is or is not acceptable would be good information because there is another area in which we can see only an increase in the future in the number of these collaborations and where it would be very good to be able to head of some of these problems.

Then there were some very special issues that I would just like to urge the subcommittee to consider giving some sustained attention to as we move through the list of our tasks over the months that will follow.

The NASA report is much more extensive than many because they had, in fact, convened a group to advise them specifically on how to implement federal protections in light of a particularly sticky question and that is the requirement that one "volunteer" to be a research subject as a condition of employment as an astronaut because of all of the human subjects research that goes on as they measure all the various things that happen to human bodies when they are exposed to extended periods in space.

And I commend them for having put in that much effort and having convened the people that they did. They had some very, very good people working on it. They come out with a list of procedures that are designed to allow astronauts to withdraw from the research endeavor but that will, in turn, have an impact on the range of missions for which they will be eligible to participate in the future.

This is a solution that attempts to balance needs for research, needs for astronauts, needs for respect for autonomy, et

cetera. But what we have no clue about is how well this works. I mean, as it stands one could argue the principled resolution of this policy. But even without having to do that one could simply ask how are the astronauts themselves reacting to it and do they feel free to withdraw in the places where it is supposed to make them feel free to withdraw and do they not?

I suspect that we may get answers that are stratified by age, since the older members of the NASA force I suspect were mostly coming out of the military instead of the civilian way of aviation and training, et cetera. We might find that people who have not gone through the military do not necessarily feel as comfortable being as constrained in their choices.

I would like to just single that out for attention because it is an unusual thing for participation in research to be a condition of employment. And having personally been in that situation as a student in which condition of my appointment as a research assistant involved having to give blood every morning to supply the blood I was working on, and not being thrilled about it, I have a special kinship with these astronauts who have to go through this in order to keep their jobs.

A second area I think that needs to be blocked out for some kind of special attention, and I happily accept some guidance on this, has to do with national security issues. First in the area of the Department of Defense report.

The Department of Defense report at first shocked me because it made absolutely no reference to the experience with the veterans who were given prophylactic vaccinations and prophylactic oral

therapy for chemical and biological agents during the Persian Gulf conflict.

And then I had to stop myself and remind myself, no, that is right, they do not have to talk about this in the DOD report because that was not research. It was innovative therapy that was subjected to a variety of research style regulatory protections solely because these were investigational drugs and, therefore, FDA's rules kicked in.

Having actually testified on that very point it was amazing I had to kind of remind myself. Which only goes to say that this is the kind of area in which if it does not fall technically under the rubric of research, nonetheless it is perceived as research by those people who have been placed -- who have been subjected to it in the context of treatment which is -- which are the service people.

And I think that it -- I would like to recommend that we pay some attention to the follow-up on the interim rule that was worked out by DOD and FDA governing so-called emergency use of these innovative therapies in which the requirements for information and consent were abandoned under certain exceptional circumstances.

And a rule that has engendered a fair amount of criticism and some very constructive suggestions coming from a variety of places in the form of testimony before the Persian Gulf Commission and members of its own commission, et cetera, and I just do not know about the follow-up to it.

But it is so close to the research endeavor that I would like to pay attention to it particularly since there is no requirement for informed consent for medical treatment in the military at all. So that

when you have innovative medicine that begins to verge on research you are doing it against a backdrop of people who never ever have the right to refuse or consent to treatment at all.

I would like to see the CIA report and the Inspector General's report because the CIA was the subject of so many inquiries in the past and the Inspector General's report was so glowing about the complete absence of any problems from '88 to '93, and they make some very sweeping suggestions for reforms nonetheless in their procedures.

It would be very interesting to see what it is that they found in their audit as well as to find out how they went about doing their audits since it is the only real audit that I found there. I was mightily happy to find one that actually went back and says that it looked at every research protocol and every human subject and every consent form, et cetera, to see what that entails.

DR. CHILDRESS: Thanks, Alta. Any responses?

DR. MANGEL: No. I mean, it does reassure us that many of the concerns that you have identified are concerns that we also identified. I think that when you get a chance to go over the questions, hopefully, we touched on many of the things.

Particularly your comments on survey research. Our question number two, for example, is in a general way meant to get at that. Survey research is only one example of where agencies seem to be invoking exceptions to the policy. Observational research, behavioral research are other areas where I think serious questions are going to be raised as to just how they are applying them.

PROF. CHARO: Can I -- it is funny because I saw two and

I actually marked "good" in little circles. That is good. The two is -- you know, for those of you who did not catch it yet, it is the one about going into some in-depth on intake and how they kind of process these things and say what is it, is it human subjects or is it not.

I have lost my train of thought. Oh, I know what it was.

To the extent that you find yourself talking to agencies that do a lot of work on surveys or do a lot of work that they perceive as being social science instead of biomedical, as a follow-up somewhere along the way for those that think that the procedures that are in place now that govern social science and biomedical research both, and then just rank them by the degree of risk and have expedited procedures for various less risky things, explore with them why if they are suggesting this why they are suggesting there ought to be a distinction made between social science and biomedical research. How they would possibly draw that distinction cleanly enough that it would not create another interpretative problem and what different procedures they would be using.

Just so that we can evaluate their responses better and understanding what they are suggesting. As well as going back and seeing whether or not unbeknownst to some people in the middle of this whole administrative mix there were ways to achieve exactly what they wanted to achieve under the current regs.

DR. CHILDRESS: Alex?

PROF. CAPRON: I have a couple of generic suggestions for you. One of which I think you already feel you deal with but I just point to the Veteran's Administration response as an example.

One of the questions that arises is the need for that centralized interpretative body and there is the interagency coordinating committee now. I was struck in the VA response that they are say boasting in response to questions, some times in response to the same question, on the one hand this is the sort of thing that would require changes in the federal policy and the VA will work with whatever policy changes come along. Basically we are happy to do it just we look to some broader group. And on the other hand they seem to be making changes to specific areas on the question of consent.

They seem to suggest that something is happening there and then on the question of compensation for injuries they say the VA is preparing regulations to provide for the compensation of research subjects who suffer injury as a result of participation.

So something -- the first question has to do with just how this -- any particular agency you are talking to views their own role in developing innovations versus the need for the leadership to come from some central body and how they distinguish. I mean, why are they moving ahead on one topic and say, well, we will just wait for everybody else to get together on the other topic.

The second question is specifically on this issue of compensation. I was very interested to see that they are looking at that. It is a topic we have said we want to look at. What are they doing? And I think you should also find out from other departments have any of the rest of them moved ahead on the compensation front? I did not see a question. Again, Joel, we have just looked at these.

The third thing is I want to read you two statements. In

response to this issue of improving on the three elements of current federal system this is the response from the Veteran's Administration.

The VA already has adequate policies and procedures in place for ensuring that human subjects -- human research subjects are protected, that sanctions are applied to investigators violating human subjects rights, and that all research conducted by VA investigators regardless of source of funding is reviewed and monitored by appropriate groups. That is in response to question 13. And in response to -- or recommendation 13.

In response to recommendation nine they say VA operates a well organized program to promote ethical practices in all aspects of health care delivery, including health research. The National Center for Clinical Ethics is responsible for the broad aspects of biomedical ethics and the Office of Research and Development provides policies, procedures and oversight for the protection of participants in VA research.

Now we know from revelations about what has happened at the West Los Angeles VA and other VA center, in Brooklyn I believe and so forth, that there have been examples of egress abuse of subjects. That is revealed at more or less the same time as we get a letter dated January 30th, 1996, with these assurances in them.

I do not want to pick on the VA alone but a question that I would ask of any of these agencies is how is it possible for you, what system allows you reliably to make statements like this that we should believe? Because as my fellow commissioners have heard me probably ad nauseam I am very concerned that we not issue a report which simply

says everything is being complied with, or here is the problem, you know, but it is at the level of paper compliance or paper noncompliance. I am concerned with real compliance.

If an agency can give us this answer in the face of this record that we know which is just as a result of some lawsuits being brought and some investigative journalists, who knows what is really going on out there. How do we know from every other department and agency that we are not going to get paper answers like this that bear little relationship to reality. That is my concern.

I hope that your process by digging into what is happening will either lead us to the conclusion that we have well intentioned people, again to use Eric's notion, people who want to do good, but whose system is set up in a way that they have no real way of telling us that their agency is not sitting on the top of a can of worms that is just as bad as what may have gone on in some of these Veterans Administration hospitals.

Or agencies that have found ways to tell you much more reliably, yes, we know, we can tell you how many subjects, we have looked at them, we have looked at the protocols, we have people who go out, we have spot checking, we do whatever. I do not know the methods they would use. But we can tell you with more assurance that what is on paper and what is in reality are the same.

So that I hope your process since you are our means out to this as a first step because one of our recommendations it seems to me will have to be about the adequacy of the present procedures.

DR. CHILDRESS: Eric?

DR. CASSELL: Well, I think, Alex, what you raise is also a very important point. What is to be a way of finding out in the future not just now? What is the way of finding out who is doing what and to which -- and which and to whom? It is very difficult to address but it is a very important matter otherwise we would get just what you want. I mean, there are people in agencies whose job it is to do that, to produce something that solves the problem on paper even if it does not have any relevance to what is actually going on.

So while I am all for education, this and that, good enforcement starts with knowledge and how is that to be obtained. How are we ever to find out what people are actually doing?

PROF. CHARO: The last article about the VA that came out of the Plain Dealer had an exchange of quotes that may or may not be accurate representations of what people said because usually they are pulled out of a much larger conversation.

But the exchange that struck me concerned the one about whether or not it was standard practice in the '80s at the time that the research was going on that was being discussed in that article, whether it was standard practice to not, in fact, tell people about the fact that they were about to go through a withdrawal period and the significance of that withdrawal period.

And the quote from a VA representative was that it was standard practice and the quote from the OPRR staff person was that that was not what the rules say. "It was not standard practice and by God nobody then in the '80s should have thought that that was appropriate standard practice."

That exchange is enormously revealing of the enduring problem of interpretation of these rules. It is part of this problem, Alex, you are talking about in terms of actual protection. It is only one part of it because the other part has to do with many other aspects of processing the paper and getting information out to people. But just an understanding of what the basic terms like informing people, getting their consent or their assent, et cetera, means in these agencies.

If find myself wondering whether with the VA or perhaps with another agency that is not in the spotlights that there is not the risk of litigation that creates an incentive to not speak. But if it is possible to simply work with a single agency, follow it through several protocols, and try to go in a very step-wise fashion through the procedures and see how they, in fact, are being operationalized.

I would even suggest that it be done not with NIH or FDA or any of the agencies that have lots of elaborate procedures at hand already but with the ones where it is more likely that there is real variability in how they understand these rules because they have less frequent contact with human subjects research or because more of it is extramurally funded and they are, therefore, taking on faith the findings of external IRBs, whether they are academically set or they might be private IRBs that are servicing private contractors who are bidding on contracts for these agencies that do extramural stuff.

Maybe either side by side, before or after, in lieu of, I do not know, a kind of across all agencies set of questions about all things might be an opportunity for more kind of anthropological approach of some great detail at walking through this process of identifying the

points at which we are seeing the breakdowns so that it is easier to tell whether the problem is in enhancing current operationalization for some set of interventions or if it is that the policies themselves are really not capable of operationalization and need to be changed.

DR. CHILDRESS: Bill?

DR. FRIEDMAN: It certainly is interesting that I was not clear how much work I would have to do and now it is very clear. It is a whole lot. I am very excited about this. I have just come on this morning. As you have seen the questionnaire, I have seen the questionnaire this morning and I like the questionnaires too. The reason I am going to make some comments is to amplify and then ask for some advice.

What you have been talking about in some of them is what are the boundaries of research and other activities like survey? That clearly is within research but that issue. Quality assurance is a big question that those of us in the Indian Health Service scratched our heads about and we think we understand the regs and we actually ask other people as well.

Program evaluation is the same thing and again when is it being done internally, quality assurance just to, in fact, improve the program and not for generalizable knowledge versus the very same activity with the very same questionnaires or whatever that is used for, in fact, some sort of generalizable knowledge? The same thing with program evaluations. We need to look at those boundaries.

Another one that I would like some advice on is should we be looking at the other boundaries? Children and mentally impaired?

Some of the things you are talking about right now that are not covered by the Common Rule. Finding out whether, in fact, they have human subjects in these other departments that fit into those and is that important for you all to know?

PROF. CHARO: Yes.

DR. FRIEDMAN: Another question I have is something that the regulations do not address very much but I think perhaps is increasingly -- not increasingly important but perhaps we realize it, is what happens when there is a failure of the system to protect subjects? The idea is that we in general, you know the emphasis is to have 100 percent effective prevention of problems with human subjects. We are human organizations.

I do not know of any human organization that is 100 percent effective at compliance or doing anything. Therefore, what is in place or how do people handle when they find out a possible problem, and is that part of the responsibility of the system to try to make whole perhaps the situation, reparation? Whatever terms you want to use. So I would like to know if you think that should be in there.

And then just an observation. I think question 14, my guesstimate as I try to think through what this talking with people is going to be about and how it is going to produce information, question 14 is, "What improvements do you think could be made?" It is often a way actually to get at problems. I would see that as a very important question to try to understand what needs to be done which is after all what you are -- what I assume is your purpose.

So I would like to know if you have any comments about

that.

DR. CHILDRESS: Thank you. Alex?

PROF. CAPRON: Yes. I would think that information from the agencies will prove useful in addressing some of those conceptual questions but I have a sense that work will have to be done elsewhere on them as well. I would expect that the agency officials involved would be very useful to us if they can provide information about what is going on in their agency. It may or may not be that those are the right people to expect to examine some of the more global issues. Their understanding of what they think research is, is going to be very important.

The difficult question of what do we mean by generalizable knowledge and if a proprietary system is doing research on a "quality assurance" sort or research to find the most cost effective way of delivering care without a detriment to human well being or whatever. Is that not research because they do not intend to publish it?

To me the phrase "generalizable research" simply means that you are going to come up with some conclusions that apply to people other than the people you have just studied. And the notion that it has to be generalizable in the sense of publishable information that you are going to put out in the scientific literature had never occurred to me that that was the limit and limitation on it but maybe it is.

I mean if I am going to a health system and they are doing a quality assurance in the sense of simply making sure that the people are delivering to me the drugs that they are supposed to be delivering and checking off, that is part of routine patient care. But if

they are manipulating the kind of care I get to see some change in the system I want to know I am involved in research.

Now maybe it goes well beyond the federal system and it would only come up in an Army hospital or some other place where the government is delivering care. Most of what I am concerned about is in the more proprietary realm but it still seems to me like research even though it is proprietary. But that is a point on which you and I, and a lot of other people can have a discussion. I do not expect to get major answers from that from the people who are telling you how the rules are working but anything they have to say about their agency's experience on questions like that will be useful.

DR. FRIEDMAN: I just wanted to comment. I think that there is no question in my mind that, yes, we need to be -- as I think has already been said -- we need to be talking with the agency heads and people up above. But after reading the book Bureaucracy by James Q. Wilson, what are called the operators, the rank and file employees who are doing -- actually working in human subjects protection there is also a different perspective and knowledge.

PROF. CAPRON: Yes.

DR. FRIEDMAN: And will be coming.

PROF. CAPRON: Yes.

DR. CHILDRESS: Okay. We want to bring this to a close fairly soon even if we have to carry it over to the afternoon so we can get some lunch before we get started again.

PROF. CHARO: What is on the table for information requests is rather vast and I fear that this is now becoming a task so

large it will not be doable in any time frame that is going to be useful.

DR. FRIEDMAN: Which information request?

DR. CASSELL: What is asked for here?

PROF. CHARO: All these questions and all the other things we are talking about and how you have these conversations, and I am wondering if I can urge you to just take into consideration the following kind of tiered approach:

To start by trying to get some basic demographic information. We do not yet know how -- for intramural research for which there ought to be records because every agency is committed to having an IRB to cover its own intramural. How many protocols have they had in the years X to Y? How many subjects have been enrolled? How many have been completed? How many hours do the IRB meet? How many people did they have on that IRB? How many FTEs were staffing it? How many FTEs have been devoted to supporting it in other context? Just to get a gross estimate at the intramural level of how much research the federal government is doing and how much effort is being expended at trying to make sure the research is done appropriately.

With regard to extramural I suspect that -- I would like to get exactly the same information. It is going to be dramatically more difficult because I suspect based on some of the responses that they are not even going to be aware of how many contracts they have let that have, in turn, required an IRB because it will be at the level of a project manager who is 16 levels down from the person who is your contact person. And yet that fact, the fact that they cannot tell how many

research projects are going on and how many people have been enrolled is something I would like to know. How frequently is that an issue? Because without this kind of stuff it is hard to even know where one might want to help direct attention for the second tier.

So I just want to throw out the possibility of a much more modest level of inquiry, organized inquiry for the first intervention, and then move on to these more subtle questions about how they go about doing this just to get some basic numbers. How many dollars are we spending per human subject in the federal government to protect people? Is it -- you know, is it a penny, is it ten cents, is it ten dollars? I do not have any idea.

PROF. CAPRON: Alta, I do not think that the stuff that is on the list we have been given is optional for us at all. I think -- I totally agree with the amendments you have made to it about knowing numbers, et cetera, et cetera.

PROF. CHARO: Right.

PROF. CAPRON: But this is -- in effect, if the agencies have all wonderfully and fully complied with the request of the President on October 3rd, 1995, we would have the answers to this. These are more -- is the attempt by conscientious people to whom we are still greatly in debt I should say.

DR. DUMAS: But she is not suggesting -- her recommendation is not instead of this.

PROF. CHARO: I did not say it was optional.

PROF. CAPRON: I thought you said you did not think we could get this in time so let's get something else in time.

PROF. CHARO: No.

DR. DUMAS: No.

PROF. CHARO: In time to begin to move forward with any further -- no, I would like it. I am asking --

PROF. CAPRON: Like at the July meeting we sure as hell better have answers to this.

PROF. CHARO: By what meeting?

PROF. CAPRON: The July committee -- our next -- the next meeting of the commission.

PROF. CHARO: Right. But I would love to know way earlier than July how many human subjects the federal government enrolls. I mean, is it possible to get information in a tiered fashion?

PROF. CAPRON: No. We have already been told they do not --

DR. DUMAS: No.

DR. CASSELL: We are going to get --

PROF. CAPRON: I mean, we have already had the answer to that, Alta.

PROF. CHARO: Really?

PROF. CAPRON: They do not know.

PROF. CHARO: Really? Where did you find the answer?

DR. CASSELL: They do not know.

PROF. CAPRON: Gary Ellis told us the first time. They do not have --

PROF. CHARO: Gary's office does not know because Gary's office does not have the jurisdiction to track it. If we go to each

agency and say, "You have an IRB, tell us how many protocols did you approve --"

PROF. CAPRON: Oh, inside --

PROF. CHARO: Yes.

PROF. CAPRON: Oh, the inside stuff because that is --

DR. CASSELL: Well, but it is not either/or. Then you want to add that to this?

DR. DUMAS: Yes.

PROF. CHARO: And I am asking if we can do that first so that we can just get a handle on the magnitude of what is going on in each agency.

PROF. CAPRON: But that is not the external stuff. The external stuff is the iceberg. You are talking about what is visible in the -- because it goes on in federal institutions and it would be, of course, revealing if the VA could not tell us how many subjects they have enrolled.

PROF. CHARO: Maybe we should do this in the afternoon so I can restate it so you will understand what it is I suggested because you are still not repeating back what I suggested.

DR. CHILDRESS: Gary, do you want to respond?

DR. ELLIS: No.

(Laughter.)

DR. CHILDRESS: Well, but would you even if you do not want to?

DR. ELLIS: Gary Ellis, OPRR. To the best of my knowledge, and I would be in a position to know, there are no data

nationwide as to the number of human subjects in research, period.

Alta had asked a question about the number of subjects in intramural research, agency by agency, and I would not know if agencies have that information.

PROF. CHARO: The second question was agency by agency since the ones that sponsor extramural research, they have contracts, they have documents that say we have a contract to do X. In those contracts it is -- it does become clear whether or not an IRB is needed at some stage. To the extent some may actually be able to tell us anything about the extent of their extramural research, great.

PROF. CAPRON: I suspect -- I agree we should look for that information. I gather it has not been available. I fully support the notion of looking for it. I have no reason to believe, Alta, that that information will come more quickly than the information to these questions. I think we should be moving ahead on all fronts equally.

I took your first comment to be you did not think we would get answers to this question in time and you were asking to prioritize those other matters.

DR. CASSELL: That is what I thought, too.

PROF. CAPRON: These questions are the essential questions. We should have had answers to them months ago. We do not have answers. Certainly by the next meeting of the commission we should have as full answers as our hired and volunteer staff, and our newly appointed staff if we get up and running, can get for us on these questions. They are essential to completing what looked on the face of it the most basic mandate we were given which is what is the federal

government now doing on paper to protect human subjects, much less knowing what actually is working by way of protection.

DR. CHILDRESS: Gary?

DR. ELLIS: Thank you, Mr. Chairman. I would just like to offer the observation that I do not believe that establishment of the number of human subjects involved in intramural research or in research globally will materially affect your thoughts or decisions on how to protect human subjects in research.

DR. CHILDRESS: Thank you. Joel, Emily, Bill, would you folks like to respond to anything at this point?

DR. MANGEL: Yes. I was just going to say that it may be that if we pursue the questions and the process that we propose we may come a long way towards answering your questions. We will at least, if we do our job right, have a handle on the magnitude of the research that they are doing and from there we may be able to take the next step and so it may be that we will get to where you want us to be anyway.

PROF. CHARO: Okay.

DR. CHILDRESS: Bill?

DR. FRIEDMAN: Just another comment. I think that probably by my very first sentence, probably to do what needs to be done requires more resources than at this table. I have some ideas on getting resources in time to get it done by the time you need it.

PROF. CAPRON: Right. I am sure it does.

DR. CHILDRESS: Joel and Emily, we thank you for what you have done.

Bill, we look forward to what you will do in this also.

All three of you, we are really grateful to you.

Any last questions or comments before we take a break and gather again at 1:30? We will be running thirty minutes behind so we will have to start right on time and be ready to finish up.

(Whereupon, a luncheon recess was taken from 12:27 p.m. until 1:37 p.m.)

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

DISCUSSION OF TOPICS FOR POSSIBLE PAPERS BY COMMISSIONERS, STAFF, OR CONTRACTORS: VULNERABILITY, JUSTICE CHANGING CONTEXTS AND PARADIGMS OF RESEARCH, COMMUNITY, ET CETERA

DR. CHILDRESS: Alta Charo, if we could get you to join us here we are going to get started. You will give us a quorum.

I am conscience about the risk of losing additional time and throwing us further behind and I know people have flights and trains to meet so I would like to get started because we have some important topics to discuss this afternoon.

In particular this afternoon we are thinking about topics for possible papers by commissioners, staff or contractors relating to some general concepts we talked about earlier as well as some other issues. The first is on vulnerability and the second is on justice and then the third and fourth are on changes in research, research paradigms and community.

Vulnerability is a theme which emerged earlier in our discussions as a possible way to orient a number of our deliberations in the area of human subjects research. Even if it does not finally succeed as a general category for interpreting all of research involving human subjects it certainly will remain important for particular populations and groups.

This is a topic that Arturo Brito and Diane Scott-Jones have focused on in particular in helping us develop our reflections. So I am going to ask Diane to kick off the discussion by introducing our guest

for the afternoon.

DR. SCOTT-JONES: Okay. I am delighted to --

DR. CHILDRESS: Part of the afternoon I should say.

DR. SCOTT-JONES: I am delighted to introduce to everyone Professor Celia Fisher. Celia is professor at Fordham University and she is director of the graduate program in applied developmental psychology there. Celia has quite a long history of work on issues of ethics in research and she has taken an empirical approach to ethical issues by studying people who are themselves potential participants in research and asking them what they think about the ethical issues that we are concerned with.

She has also studied researchers as well and that research is reported in a book entitled Ethical Issues in Mental Health Research with Children and Adolescents. It actually gives case reports of researchers and the ethical issues that they are dealing with.

Celia has also chaired APA, the American Psychological Association's Task Force to Revise the Ethics Code for Psychologists and she has also chaired the Ethics Committee of the Society for Research in Child Development.

So Celia is going to talk with us and then we are going to have a discussion on some of the issues that she deals with in the relationship of researchers to the participants they study.

Celia?

VULNERABILITY GUEST DISCUSSANT

DR. CELIA B. FISHER, FORDHAM UNIVERSITY

DEPARTMENT OF PSYCHOLOGY

DR. FISHER: Thank you, Diane.

First, I will make a brief presentation and I have also provided the committee with a questionnaire that we gave out to investigators in the NIMH study, as well as a brief questionnaire that I have developed on research on Latino mother's attitudes toward different ethical issues in guardian consent in this particular study for research on high risk sexual behavior in Latino adolescents.

The goal of this brief presentation is to propose that the ethical demands of a scientific investigation are best understood when viewed within the context of a given study and from the perspectives of those who design, implement and participate in the research. Healthy adults, adults with physical and mental disabilities, children and adolescents and individuals from diverse economic and cultural backgrounds react differently to controlled procedures and their perspectives can differ from those of well-meaning decision makers.

Creating federal guidelines based upon abstract moral principles without considering the expectations of and special relationship between investigator and participant may actually decrease the adequacy of ethical procedures. As such, national guidelines aimed at promoting the rights and welfare of vulnerable research participants need to enable investigators to make ethical decisions that facilitate constructing the best procedures possible within a given situation.

Researchers applying the scientific method to describe, explain and enhance the status of individuals with physical, psychological and social vulnerabilities are encountering ethical dilemmas to which current federal regulations offer incomplete answers.

When the goals of science and ethics appear to conflict investigators studying vulnerable populations draw upon their own moral compass, the advice of colleagues, and recommendations of institutional review boards to make decisions about ethical procedures that will have immediate and possibly long-term impact on individual subjects, their families and the communities they represent.

Historically these decisions have been grounded in two meta-ethical traditions. According to the first tradition, utilitarianism, an action is ethically appropriate if it leads to the greatest good for the greatest number of people. Utilitarianism can thus promote a value structure in which potential benefits to society take on a higher priority than concrete and measurable risks to research participants.

According to the second tradition, deontology, an action is ethical if it reflects inherent respect for the dignity of persons. With its focus on the universality of moral principles deontology can lead investigators and IRBs to determine which research procedures are ethical without consulting members of the population that will be studied.

Thus both utilitarianism and deontology have the potential to minimize a scientist's special relationship and subsequent moral obligations to individual research participants and foster a psychological distance between scientist and subject.

In the absence of knowledge about what research subjects think about ethical alternatives investigators have little ethical guidance when confronting such questions as:

Does prevention research requiring public identification

of risk factors in persons with cognitive, physical or psychological disorders violate their privacy or lead to social stigmatization?

Is requiring guardian consent always in the best interest of minors or individuals with cognitive impairment?

Under what conditions is it ethically reasonable to use placebos, control groups and randomized assignment to evaluate the efficacy of a treatment for persons identified with physical or mental disabilities?

When is payment for research participation coercive for the cognitively impaired or those from impoverished backgrounds and when is withholding of such payment inequitable?

Moral arguments for the duty to consider participant perspectives in ethics and science decision making derive from a synthesis of principle based justice ethics and relational base care ethics.

The justice perspective emphasizes moral agency based upon principles of mutual respect, beneficence and fairness. It stresses impartiality and distance from the scientist's own interest and her or his connected-ness to participants. The ethics of care emphasizes the duty to interact with research participants on their own terms and to respond to their needs as they extend over time.

A justice care framework recognizes that ethical principles can mediate our understanding of participant perspectives without placing a priority on how investigators interpret these principles over the moral frameworks of participants and that respecting research subjects involves responding to them on the basis of their own self-

conceptions.

The justice care perspective gives rise to several moral arguments for including the views of prospective research participants and their families in federal regulations and ethics and science decision making.

First, formulating regulations and ethical judgment solely on the basis of experts in the scholarly community, the opinions of IRB members or an investigator's own moral compass risks treating subjects as research material rather than moral agents with the right to judge the ethicality of investigative procedures in which they are asked to participate.

Second, failure to consider participant's points of view can lead to acceptance of research procedures causing significant participant distress or to the rejection of potentially worthwhile scientific procedures that subjects and their families would perceive as benign and/or worthwhile.

Finally, understanding the point of view, needs and expectations of others can enhance an investigator's own moral development for a better understanding of the reciprocal relationship between the participant's expectations and the scientist's obligations.

Another aspect of this relational perspective is the importance of grounding ethics and science principles and federal guidelines in the practical day-to-day experiences of researchers. As my colleagues and I found in our recent NIMH survey investigators striving to meet the dual obligations of protecting participants and producing valid scientific knowledge have developed innovative ways of identifying

and minimizing research risks without forfeiting the integrity of their studies.

Researchers studying vulnerable populations can provide ethicists, policy makers, members of IRBs and citizens an enhanced understanding of the ethical challenges that arise during the actual and design and implementation of human subjects research, the barriers that current ethical guidelines sometimes place on good scientific and ethical practice and the practical and innovative steps that have been taken to meet these challenges.

The practice of science without guidance from ethical principles is morally blind but the establishment of federal guidelines without relevance to real world applications will be empty.

If one believes that knowledge concerning participant perspectives is essential to good ethical decision making, how does one go about generating this knowledge? To engage individuals in a morally ambiguous study for the purpose of eliciting their reactions is ethically problematic since it exposes persons to what the investigator believes may be the procedures which potentially violate their autonomy and welfare.

To give prospective participants open ended questions concerning research ethics is equally problematic since it asks individuals to provide spontaneous and decontextualized responses to moral questions which require informed deliberation.

Over the years my colleagues and I have developed empirical methods based upon a co-learning model of scientist participant relationships. Individuals in our studies learn about how the

scientific method is applied to examine questions of societal import and are introduced to areas of current ethical concern. We, in turn, learn what prospective participants think about specific ethically relevant issues, their views on whether or not certain types of studies should be conducted and the moral frameworks applied to their decisions.

We have established dialogues about guardian consent procedures with Hispanic mothers, about confidentiality of research with urban adolescents, and about randomized clinical trials and deception research with young adults.

Our endeavors have challenged stereotypes about how participants view ethical procedures. For example, in one study we found that urban high school students do not endorse maintaining confidentiality when during the course of research an investigator discovers a teenage subject is a victim or engaged in behaviors adolescents themselves perceive as serious problems. The teenagers' responses indicated that they saw the investigator as having a moral role in relationship to their problems. Their views raised heretofore unasked ethical questions concerning the consequences of scientists failing to fulfill this role.

For example, an investigator's failure to help may unintentionally communicate to a troubled high school research participant that his or her problem is unimportant, that no services are available, or that knowledgeable adults cannot be depended upon to help children in need.

A relational ethic of scientific responsibility and care which considers the interpersonal dimensions of the scientist-participant

relationship can lead to the examination of other under explored areas of ethical inquiry.

For example, is the current emphasis on harm avoidance sufficient ethical justification for conducting research on mentally infirmed or marginalized populations if it places the ethical burden on participants or their guardians to demonstrate that they have been harmed and away from the investigators who need not demonstrate that their research will result in any good.

If research findings can have direct impact on public attitudes and policies directed to individual research participants, their families and communities? To what extent should group stigmatization be considered in determining research risks and should the nature of such risks be described during informed consent? Who should represent participant and community interests on IRBs?

When do tests of competency to consent for research decisions place an unjust burden on those with identified mental deficiencies? How can risks be better defined across diverse populations so that norms based upon healthier advantaged persons do not over include or exclude vulnerable populations from research?

What role should the altruistic benefits of research participation play in the cost benefit calculus for research presenting greater than minimal risk? And given the scandal surrounding the Tuskegee and Willowbrook studies, the Government Radiation and UCLA Schizophrenia experiments, and the recent controversial Adolescent Violent Research Initiative, how can scientists win the confidence of vulnerable persons and their appreciation of the potential positive value

of research?

Including participant perspectives and the practical concerns of scientists conducting research with vulnerable populations and the establishment of federal guidelines raises its own ethical challenges. For example, when including participant perspectives in the ethical evaluation of federal regulations bioethicists need to address issues raised by the potential tyranny of the majority.

Principles of respect, beneficence and justice informed by participant and investigator perspectives can guide policy makers in their struggle with the question of whether a particular procedure can be justified if a substantial or even small minority of perspective participants believe the cost of participation outweigh potential benefits or that procedures selected are in conflict with individual moral frameworks.

Consideration of participant or investigator opinion also runs the risk of accepting descriptions of ethical decision making as prescriptions for ethical decisions. The fiduciary nature of the scientist-participant relationship obliges the investigator to take ultimate responsibility for the welfare of research subjects.

A relational perspective based upon the ethics of both justice and care proposes that an understanding of participant views can assist but not substitute the ethical decision making obligation of individual scientists and policy makers as moral agents. Thus the opinions of those from the scientific and participant communities need to inform but not dictate federal guidelines and ethics approval or disapproval of research practices.

In conclusion, attention to the interpersonal nature and obligations inherent in the scientist-participant relationship expands ethics and science decision making to include the importance of intersubjectivity, particularity and context, and moves scientists toward a reinterpretation of their own moral agency.

The relational perspective enhances the ability to engage scientists and research participants as partners in creating federal guidelines reflecting both scientific and interpersonal integrity. Scientific ethics is a process which draws upon our human responsiveness to those who are participating in research and our awareness of our own boundaries, competencies and obligations.

If becoming a moral subject is the critical moral task for all persons then recognizing that morality is embedded in the investigator-participant connection is the essential moral activity of human subjects research.

Thank you.

DR. CHILDRESS: Thank you very much.

Okay. Let's open it for discussion. Alex?

PROF. CAPRON: I want to thank you for sharing the model with us and the relational model I think has a lot to contribute to our thinking about how the process can be improved and the design of experiments and in flushing out the relevant ethical concerns. I had a couple of sort of basic questions for you.

One, I did not understand the basis of your critique of deontology. I certainly understand the critique of the utilitarian viewpoint. But as I understood you, you were saying that the problem or

the way in which deontology stands in the way of a relational perspective is its focus on the universality of moral principles. And it certainly attempts to be universal. I mean that is one of Kant's major intellectual moves is that insistence on universality.

But I do not understand that ethical precept as saying anything about the universality of the subjects, that is to say the notion that you are obliged with all subjects to respect the integrity and dignity of the individual and have respect for persons does not insist that the individual wishes, needs, ideas, et cetera, of that actual subject would be irrelevant.

DR. FISHER: I think what I was trying to say is that the deontological perspective in some sense allows a group of people like us right here to deliberate and an IRB to deliberate about ethical principles without assuming that we need to be informed in order to best understand and articulate those principles in any given research context without the perspectives of those people to whom the research is going to engage.

PROF. CAPRON: I guess I would see deontology insisting on just the opposite, that if you are going to respect persons, and the persons we are talking about your potential subjects, then you would need to take more attention than we have in the past. In other words that your model is a way of having research ethics fulfill its deontological obligation rather than being in distinction to it.

DR. FISHER: I think in the ideal you are correct and in the ideal I think that both utilitarianism, justice care, deontology, all of those need to be combined. However, I think in the practice both

utilitarianism and deontology has created this distance which we see with respect to how IRBs are set up. We typically have one community member and that community member is supposed to reflect the perspectives of all the different various participant populations in the area. So I think in principle I agree with the ideal but the real has enabled this kind of distancing.

PROF. CAPRON: On the agenda the topics which are identified for us in this session are these generalized concepts of community and vulnerability, and justice, and so forth. You are listed under the vulnerability heading.

Do you have any thoughts specifically on the subject of vulnerability because what you were producing for us seems to me to be in the relational model in particular something which is equally applicable to any population? You did use the term "vulnerable populations" a couple of times but I did not hear from you any sense of what the factors are that you would use in deciding whether there is such a category of vulnerability and how it is constituted.

DR. FISHER: Well, I do not know if I can define what is vulnerable. I think that one of the things I have been struck by both in the conversations here and in conversations that I have engaged in as well is how we tend to categorize those that are vulnerable as if they fit into a category. Earlier on when the group was discussing competencies to consent I think was an example of something that I engage in as well but we all tend to define and begin to identify those as vulnerable and they become a category to be acted upon as opposed to just another person or moral agent to whom we may want to adapt procedures.

So I think that vulnerable, we misapply that term to encapsulate a person who has various abilities and we do so many times because of legal precedence which with respect to who is considered competent to consent in the legal arena. And I think one of the things I tried to point out was, and in some research that I am conducting now on the ability of adults with mental retardation to give consent to treatment, is that I think sometimes we hold those who are considered legally incompetent to consent to an undue and unfair standard.

We assume that those who are considered legally competent to consent always make excellent moral judgments or abstract decisions, you know, going with the Appelbaum and Grisso (?) model, we assume that those who are not labeled incompetent are making these decisions at the highest level. What my research is beginning to demonstrate is that is not the case but at the same time we can easily say that we can use a guardian or proxy consent for someone who is identified as mentally incompetent because they do not reach that high level.

PROF. CAPRON: Okay. I will let others comment. I mean, I would say for myself I do not make that assumption.

It seems to me that the assumption that the law makes is if you are presumed to be competent what that means is it is presumed that other people may not interfere with the decisions you make simply because they disagree with them not that you are operating at any exalted high level that you are a Socrates or something in your thinking. It is simply that you do not have such disabilities in making decisions for yourself.

DR. FISHER: But I think you are absolutely right and I think that is the issue that when we label somebody as lacking competence we are by definition saying that if we do not agree with their decision that we can then have someone else make that decision for them.

PROF. CAPRON: Yes.

DR. FISHER: And I think that sometimes people who are not labeled incompetent to consent will also make research or treatment decisions that the practitioner or scientist would not agree with.

PROF. CAPRON: Yes.

DR. FISHER: But would not supplant their decision making for that person's decision making.

PROF. CAPRON: That is right. It is almost a conclusory thing that -- I mean, to interfere is to announce that you believe the person is incapable of making that decision.

DR. FISHER: Right. That is right.

DR. CHILDRESS: Eric is on but I want to get Diane in to respond directly.

DR. SCOTT-JONES: I wanted to respond a little bit to Alex's question about vulnerability and I just wanted to reflect a bit on our previous discussion. When Arturo proposed the concept of vulnerability that might be useful as one for us to use to frame some of the work that we will do on the commission there was some objections raised to the notion of vulnerability and one objection was that the idea of vulnerability locates within the individuals the problems that might occur in the research setting and there was some thought that the

problem is not inherently within the person but it is in the relationship of the researcher and the participant.

It is in the manner in which the researcher goes about enlisting the cooperation of the particular potential participant and so what Celia's work offers us is a different way of construing this. Instead of looking just at the vulnerability of the individual you place that in the context of a relationship of the researcher to the persons the researcher proposes to study.

You are right, Alex, that this model could be used to apply to any relationship of researcher to those researched, not just those that we single out and label as vulnerable.

I think it is in keeping with Arturo's original idea and that was that any person potentially is vulnerable when they set out to participate in research and there are special classes of people that we recognize as having vulnerability. So it was with that background that we sought out Professor Fisher's work for the commission.

DR. CHILDRESS: And it fits well with some of the things that has Eric has proposed, too, but we will see whether he agrees or not.

DR. CASSELL: Dr. Fisher, of course I am. I find it very congenial what you say but I am drawing on our unscheduled conversation and trying to get it on the record also. It requires investigators to have a level of ethical competence which goes beyond their, what you call, moral compass which can be very restricted. And your work -- have you got work that shows whether investigators indeed have the ability to make a relationship with a researcher that represents

more than their own interests in that relationship?

DR. FISHER: I have no data that says that and I think you are absolutely right that we as a researcher, myself, are not trained to do that and I think it is very important as we were discussing that at the entry level to scientific method that ethics is not seen as something tangential and tagged on at the end but seen as intricately involved in the conduct of good science and that responsible science takes on that joint definition of valid research methodology and valid ethical procedures.

One of the things that I might suggest would be, and something that I have done, is that just as we pilot, for example, our research methodologies we can at the same time be piloting our ethical procedures so that when we take to an IRB the research that we are doing we can also have some kind of data or perspective with respect to the responses or the adequacy of the ethical procedures that we are using within this entire research project.

DR. CASSELL: I take it that you also teach?

DR. FISHER: Yes.

DR. CASSELL: And do your students find your point of view about their obligation to have knowledge about their ethical competence as well as their scientific, are they congenial -- is that congenial? Do they like that?

DR. FISHER: My students love it. My students feel --

DR. CASSELL: They probably love you, doctor, but do they love it?

DR. FISHER: They love it because they -- my students

want to do applied research. They want to do research that matters. And so when the ethical component, the relational component of ethics is brought in it draws them nearer to the type of research that they have dreamed of doing, that that kind of research that actually reflects the voices of the participants that they are studying and may actually be worthwhile for those participants.

DR. CASSELL: Thank you.

DR. CHILDRESS: Alta?

PROF. CHARO: First, I want to make sure that actually I am understanding. Would it be correct to restate the following: That rather than worrying about persons who are vulnerable to exploitation or abuse in research what we should identify are situations that are vulnerable to abuse occurring and that those situations might arise because of many factors.

One might be the nature of the subject and some intrinsic quality about the subject like their lack of decisional capacity. Another might be because of the investigator's attributes, for example, being on a -- kind of having a financial interest in the number of patients who are recruited. And a third might be an institutional problem such as being at an institution with a weak or absent IRB so that we are talking about vulnerable settings rather than vulnerable persons.

So far I am catching?

DR. FISHER: Yes.

PROF. CHARO: Okay. Then let me ask you then how if you have identified a setting that you now think of as one that is vulnerable to abuse, and I will give you a specific example because it is a

small one and it is current.

Research on people who are in an emergency circumstance where there is no other person who can assist with the decision making for whom there is a proposal to do research on an emergency intervention.

This has been the subject of a recent regulatory change. One of the things that was included in that change was the requirement for community consultation in the development of these protocols since they are going to be implemented, for example, on the street at the ambulance and there will be no opportunity at that moment for people to refuse.

For those IRBs that are now undergoing the exercise of trying to engage in a community consultation and with that help and all the other usual things come up with a set of rules about how they are going to go about this, it seems to me that what you are talking about in your methodology is what they have to go through in developing a set of rules.

But I am not sure I really understand yet how your methodology would be applied. How would you construct a community consultation? What would you do with the diversity of opinion that you would likely receive? What would you do with the fact that you might receive 90 percent of the people in your identified group saying this is a great thing, we need it in the absence of standard therapy, and 10 percent saying no, and then translating that into operations because that is a narrow, well encapsulated example of something that might have to be ratcheted up to a more complicated situation with regard to people

with cognitive impairment.

DR. FISHER: Right. Let me try to address it three ways if I remember all the things that I was thinking about.

The first issue, I think, that you raised is -- leads me to think about who is the community. And I think that the community has several levels. When we do reach out to the community we tend to reach out to community leaders. Community leaders, although certainly a valid source and a critical source, and also -- and many times an entry level source into the neighborhood itself, do not always reflect the voices of those who will participate in the actual research.

So in your encapsulated version not only would, I believe, the researchers in what they are going to present to the IRB should have gone to the community members but also to those who are at highest risk. If it is in a population where it is adolescent drivers or if -- you know, whoever is the highest risk from epidemiological data they should be part of that data collection in terms of their perspective.

How do you go about gaining their perspective? Well, in the handout that I gave you, which is just a small segment, as I tried to mention in my talk one of the things we have to be careful about is not giving prospective participants this broad question of what do you think the ethics are in this research. They have not been thinking about those things and to do so would really limit the information that we could get. So the kind of model that I have tried to develop is to begin the dialogue by presenting prospective participants with the ethical dilemmas that scientists and ethicists have raised about the particular situation. Get their opinions about those different perspectives and then move towards

then are there other perspectives that you see. Okay. So that is one model of doing that.

To your last question, which I have called the tyranny of the majority, I think that there is not one answer to what happens when 90 percent say yes and 10 percent say no. If we are very, very lucky and we can identify the nature of those 10 percent who say, no, we would know they would not want to do it but that would -- we would be lucky.

However, I think what it does require is a discourse with both those 10 percent and the 90 percent. What is the reasons why the 10 percent say no? Are they legitimate? Should they be informing perhaps the way we are asking the question or maybe we can modify the ethical procedures somewhat so that we would increase that majority and in some way address the minority concern.

So it is constantly evolving. We do not stop. It is a constant process of getting feedback and information from prospective participants, changing our methods, going back and finding out how those methods have worked or what the prospectives are.

PROF. CHARO: Would that then argue against a regulatory model in the context of the cognitively impaired? Because what we have heard so far have been specific suggestions for regulations that spell out what kind of research can be done, what level of risk based on what levels of impairment, assent, consent and prospects for risk and benefit. They often are very specific about having surrogates do this or need for guardianship for that, durable powers.

This is a kind of approach that is very rigid. It does not permit the kind of constant evolving that you suggest would be better.

Its advantage is that it is standardized and that for -- it does not permit a devolution of protection that can also occur when there is a constant backing and forth-ing of discussion and a great deal of self reflection and self determination about how you are going to go about doing these protocols when you leave it up to the investigators and their local groups to decide each time ad hoc based on their accumulated experience of how we will go about dealing with research in this vulnerable setting.

DR. FISHER: I think I am not prepared to make a decision about that or even have an opinion about whether or not there should be this subsection that directly addresses the cognitively impaired.

However, I do think it raises the larger issue that you raised this morning which is should we -- should the commission recommend in some sense guidelines based upon a presumption of prohibition of research which in some sense says that protection of human participants at all costs and research is looked at as secondary or should protection of research participants be looked at in a difference sense, research except?

So I think it is addressing a broader issue and I would also say that the special subsection on children -- I am not sure.

My impression is that investigators from the survey that I did for NIMH do not feel that those guidelines have protected children, that they are -- they feel that those guidelines have made children orphans of research especially in psychopharmacological research.

So once again I am not prepared to say that those specific kind of guidelines should not be there but I think that it would be

a wonderful thing to think of what an alternative would be if we did not rigidify and in some sense stigmatize a particular population which may mean that they do not -- which may challenge the justice equitable aspect of them having equal access to research.

DR. CHILDRESS: Could I build on that? If I heard you correctly then the relational model that you proposed does not necessarily rule out regulation in particular cases? That is to say you might make an argument because you do include other kinds of considerations. You have justice care, you have utilitarianism, you have deontological considerations.

So all those are present but when you take this particular model it is going to push in a certain direction and you are going to try to encompass a lot of things. You are going to be open to a process view as much as possible but that certain kinds of circumstances may well warrant the regulatory model. Is that correct?

DR. FISHER: Right.

DR. CHILDRESS: And then what you have to do is look more carefully at that.

DR. FISHER: Right. And I think in terms of which of those settings, situations, persons require that needs to be based not only on our wisdom as professionals but also on information gained from those doing the research and those who are the recipients of research.

DR. CHILDRESS: Alex?

PROF. CAPRON: I wanted to follow up both on Alta's question to you and on this critical incident contributor role that you ask people to play.

On Alta's point it seemed to me that you were put in a funny spot because she was posing it as though this was a little bit more of an either/or than I suspect she really believes.

In the case of the person who is in emergency research the premise there is that there is no one who could consent for that individual and the only framing of it can be gotten, if it is not just left to the investigator, by bringing in some sort of a surrogate community to try to refine and respond. Does this seem if I were in this situation sort of a --

PROF. CHARO: It is a substituted judgment.

PROF. CAPRON: Yes. A collective judgment of the norms that would apply because the whole idea of giving treatment to people who cannot consent in an emergency is that it is reasonable to assume that a person would want this kind of treatment in this emergency when they cannot consent. So this is it is reasonable to assume that they would want this kind of research if they were in this kind of situation.

But in the case of the other model that we were hearing about before with the cognitively impaired you have the ability to have someone, either the individual through their direct participation or through their participation in an assent process, or someone designated by them or their natural surrogate, or parent, or whatever to participate in an individualized consent process.

But that could still have followed a process in which they and others helped to work with the researcher to make sure that the -- what really is harm is seen as harm and so forth was built into the experiment. But any individual could say, "Well, that may be a very

nicely designed experiment but I do not want my son, daughter, mother, father, whoever it is to participate in it, thank you." So you could really still think of -- they are not either/or in my mind.

PROF. CHARO: No, I was not suggesting that. It is simply that this morning there was the possibility of going down a road of trying to write some fairly specific rules in which you characterize specific subpopulations of patients and look at their exact levels of ability to communicate and look at the kind of research and come up with a set of rules.

You were talking about a matrix yourself, right?

PROF. CAPRON: Right.

PROF. CHARO: The alternative was something much more general followed by ad hoc review of protocol by protocol in which you never try to characterize things quite that precisely and these things are not completely mutually exclusive.

But if you were to adopt a matrix like approach in which based on a certain kind of competency and a certain kind of research you must use durable powers or you must use a health care agent, you cannot use a surrogate or you cannot use -- then it is not, in fact, completely consistent with an approach in which on a very local level there is a constantly evolving concept among the PIs in that center and the people who are being recruited, and the IRB about what is the best way to go about things, and you would have to move much more slowly as you worked at the regulatory level for change.

I was just trying to get a sense of kind of relative degrees of attachment here to one model or another because they really do have

different consequences.

PROF. CAPRON: One of the things that Dr. Fisher mentioned was this process of developing this new case book in effect of these critical incidents. As I understand it, it is researchers who are going to be your incident contributors. Is that right?

DR. FISHER: Well, in this book it was researchers who were the incident. In the American Psychological Association's, in the Ethics Code I am revising, one component will be the researchers. But for me obviously in the research that I do --

PROF. CAPRON: Right.

DR. FISHER: -- an incredibly important component is the research participant themselves as well as their family members who are often impacted by research.

I do want to say I was struck in some of the reading materials that were sent -- the article by Sachs who talked about the demented individuals and how they were in many instances able -- even though they did not meet levels of legal competence to consent they were able to identify if they wanted a proxy and who that proxy might be, and they were able to communicate values and preferences that I think could very well inform a commission.

I think it is important for those with varying types of cognitive impairments, depending on that level, to get information regarding altruism in the language that they can understand.

Do they want -- do they like to do good? Do they like to do something for somebody? Are they risk takers? I think that there is language that we can use to be informed also about the perspectives

that some people with cognitive impairments might take. Once again I feel very strongly it does not relinquish our role as moral agents and fiduciaries to make the ultimate responsive decision.

PROF. CAPRON: Right.

DR. FISHER: But it certainly informs us and makes that person more a person as Dr. Cassell keeps pointing out.

PROF. CAPRON: Right.

Well, I may be bringing up something that everyone else understands well but I take it that your prescription can operate at two different levels.

One is when you speak of the things that a national commission would want to know or an IRB generally in setting up the framework that could come out by discussions with people in whatever categories you are talking about and where you were reaching generalized ideas. Now in a certain way I would expect you to be a little bothered by that because your complaint about deontology was that it was trying to be universal.

I thought that the model that you were describing was something else which was actually quite specific to the investigator-subject interaction as a diad or there may be more people involved.

DR. FISHER: Right.

PROF. CAPRON: But as an individual instance and then any particular individual in that situation ought to be treated with the kind of respect that would say people looking at this field have seen these kinds of problems and I want to tell you a little bit about them and then have you reflect in light of those things and your own values how

you feel about participating, what things you would want to raise as problems that I should be aware of in conducting the study, and it is a more individuated --

DR. FISHER: Right. I think the model -- and I think within the brevity of the paper I was struggling with how to present it at both levels.

PROF. CAPRON: But you agree --

DR. FISHER: I agree. There are two levels.

PROF. CAPRON: -- with both?

DR. FISHER: One is to inform the commission and part of what may be informing the commission is maybe there needs to be some recommendation with respect to how researchers then can engage participants.

PROF. CAPRON: Yes.

DR. FISHER: So that is one level of influence on the commission. The other is the commission being informed by just those populations that are being addressed, the vulnerable populations that have been identified and their families in this task.

PROF. CAPRON: The document, the form letter that we have here, this relates to ongoing research?

DR. FISHER: No, that was what we sent out for the NIMH.

PROF. CAPRON: That is what was used --

DR. FISHER: Right.

PROF. CAPRON: -- for that book, the chapter --

DR. FISHER: Exactly.

PROF. CAPRON: Okay.

DR. FISHER: Exactly.

PROF. CAPRON: Okay.

DR. FISHER: And then what is underneath that is the model that we have been using with Latino mothers with respect to explaining to them the ethical dilemmas that have been raised by psychologists asking them to respond to those and then moving on.

PROF. CAPRON: Right.

DR. FISHER: Of course the way it is presented here it is much more of a focus group. It is much more of a dialogue but this is presented in a much more quantitative way.

DR. CHILDRESS: All right. We will need to bring this part to a close.

Would you like a final word?

DR. FISHER: Well, no, not really. I want to thank you for inviting me and that I guess I was saying both to you and Dr. Cassell that I felt that for better or worse one of the enduring aspects of the Belmont Commission was their stated moral framework which drew upon principles of respect, justice and beneficence, and in some sense reinforced the utilitarian perspective, and so I think the way I tried to frame my presentation I do feel that it would be helpful if the commission was attentive to the implicit or explicit moral framework that is communicating in any recommendations that it makes.

DR. CHILDRESS: Thank you very much. This has been exceedingly helpful and gives a lot of food for further thought as we move along in our deliberations.

You introduced as part of your discussion the care justice

perspective. In discussions that several of us have had at different points, Alta Charo, among others, has raised the question about whether rather than vulnerability we might think about justice as a way to look at some of these issues.

The three guests who are going to join us for the next part of this session are in the process of putting together a book on justice and research involving human subjects.

They are Jeffrey Kahn, who is Director of the Center for Bioethics at the University of Minnesota, the Center for Biomedical Ethics. The director of that center at the University of Minnesota.

Anna Mastroianni, who is a teacher of law and bioethics at the University of Washington School of Law.

Jeremy Sugarman, who is a co-director of the program in medical ethics at the Duke University Medical Center.

All three were heavily involved in the work of the Advisory Committee on Human Radiation Experiments with Jeffrey Kahn and Anna Mastroianni being associate directors.

I believe that was your title, right?

MS. MASTROIANNI: Yes.

DR. CHILDRESS: And then Jeremy Sugarman being a senior analyst.

Since they are working on justice I am sure they have come up with some fair way to present these materials to us in a short period of time and then be open for discussion.

I think someone -- one of the three will do it and then all three will be available for conversation.

JUSTICE GUEST DISCUSSANTS

DR. JEFFREY KAHN, UNIVERSITY OF MINNESOTA

CENTER FOR BIOMEDICAL ETHICS

ANNA C. MASTROIANNI, J.D., UNIVERSITY OF

WASHINGTON SCHOOL OF LAW

DR. JEREMY SUGARMAN, DUKE UNIVERSITY

MEDICAL CENTER

DR. SUGARMAN: It is my job today and if I say anything wrong look for the faces of Jeff and Anna as I speak with our collective voice and you will know that they will correct me when I finish.

I am going to move --

DR. CASSELL: Jim?

DR. CHILDRESS: Yes?

DR. CASSELL: Could we have him do it from that table?

DR. CHILDRESS: Okay. The recommendation was so we can see you.

DR. SUGARMAN: You can tell we spend time on staff because we are good at adjusting signs and microphones.

PROF. CAPRON: Right.

(Laughter.)

DR. SUGARMAN: We do appreciate the opportunity to share some of the work that we have been doing and in the interest of time I will be speaking rather quickly about several of the things that we are working on and we will be happy to elaborate when I am through.

As Jim mentioned, we began our collaboration together on the staff of the Advisory Committee on Human Radiation Experiments

and it is good to see Alta sporting a copy of the final report. You can see them from a long distance which is not necessarily a sign of success of advisory committees. But it is quite a text that speaks to where our interest began in the questions of justice.

As you may remember, President Clinton chartered the Advisory Committee on Human Radiation Experiments in response to reports in the media of human radiation experiments that were done without the consent of subjects. So it seemed at the outset that as we looked at historical cases we were going to be looking merely at whether or not consent had been obtained and what had happened in those actual experiments.

As the Advisory Committee began its work, Ruth Faden as the chair, we were charged with making recommendations for the future so that the abuses that had taken place in the past would not happen again. In order to do that the Advisory Committee took on three empirical projects and it was in these empirical projects that we realized that there had been some sort of a sea change that had gone on behind the notion of justice consent to one about questions of justice.

The Research Proposal Review Project which Jonathan Moreno touched on briefly this morning where the Advisory Committee reviewed 125 research proposals from IRBs around the country of approved research we learned two big lessons regarding justice. That issues about the selection of subjects were almost neglected in these documents and that there was a general over promise of benefits and under representation of risks.

Now this in isolation just from documents might not have

meant so much with respect to justice. It could have been just a quirky finding, a hazard of empirical research, but what we learned in the subject interview study where we interviewed 2,000 patients around the country at 16 institutions was two strong themes that came through the in-depth interviews.

One was an overwhelming trust. The interviewees told us that they trusted researchers. They trusted the institutions in which research was being conducted. And they trusted the enterprise of research to make sure that research was done in an ethical fashion. This trust overpowered all of our questions about consent and other issues regarding research.

The other issue that seemed strong is they participated in research because of a hope for personal benefit. Although that they could realize that there were other reasons, altruism and the like, that this notion of personal benefit and hope were quite strong.

So it seemed through a variety of these projects that there was some sense of a conflagration of research and treatment. As we talked more about this we realized that we wanted to do something on justice and at first cut there seemed to be at least two claims about justice. There was one about protection and one about access.

The initial claims were let's protect people from risks, the Office of Protection from Research Risks for example, and that IRBs and the research enterprise was charged with that oversight. Now we were hearing things like "access to clinical trials," patients with cancer, HIV infection and AIDS who wanted to be in research. That seemed quirky to us in a way if you consider the history of research and the way we teach

research ethics which involves questions of scandals and justice, and all of this.

Then there were mandates for including people in research. Now that also seemed a bit odd in light of the history of research and research ethics.

So these claims seemed in stark contrast to much of the conceptual work that we encountered as well as the policies regarding research ethics. Again the conceptual focus had been on autonomy and beneficence and these panned out to be the things like informed consent, IRBs, OPRR, et cetera.

So after thinking about this some more we realized that the conceptual work had not caught up with what was going on in the research world so we began to work on the idea for a book which is entitled Beyond Consent: Seeking Justice in Research. It is under contract with Oxford. We have a series of solicited chapters. The organization of the book is an overview of the relevance of justice to research and then the history of policies involving justice.

We then take populations and setting asking the question in each case do they raise similar concerns about justice and the populations or settings we have chosen are captive and convenient populations, children, patients, women, international research, race and ethnicity, and then asked that same question again, do they raise some more concerns about justice.

We then do some conceptual work putting all this back together and then make some recommendations to those involved in research from researchers to IRBs to policy makers.

Now basically we have a draft. Much of the book is done but the recommendations part is still wanting and some of the conceptual work still needs a little bit of attention. But basically we want to give you just a hint of our work.

First, the first cut of justice was sort of a Belmont notion of justice. There are two ideas about justice that were floated in Belmont. Fairness and distribution of burdens and benefits and equals ought to be treated equally. This follows a lot of the work on the concept of justice and biomedical ethics more generally as Professor Childress and Tom Beecham have pointed out many times.

Next we wanted to get a little bit more complicated. Here Baruch (?) Brody's chapter for the book is quite helpful. Baruch sees that it is not just two notions of justice here but that there are many values of justice that need to be balanced in a pluralistic way. He uses the language of pluralistic casuistry (?) history. His values are social need for research, benefit to subjects, and protection from exploitation and harm.

Going further, in some of the work for the conceptual chapter by Madison Powers, we look at now not values, not an axiology inherent to justice but more of approaches to justice, more theory like approaches. You will see how this plays out in light of current realities in a second. Madison defines five.

The first is a libertarian notion of justice. Individuals ought to be free to accept the risks of research. To bring that to Earth for a second we are going to give you some examples. Here women with breast cancer want an access to unproven therapy such as autologous

bone marrow transplantation.

Another approach, individual egalitarianism. Individuals ought to have equal access to the benefits of actual research participation. Here would be a familiar argument for Medicaid recipients to have access to research.

Third, group egalitarianism. Recognizing that individuals often bear burdens but groups may receive the benefits of research. Diverse individuals ought to be included in research so that the groups from which they come may derive benefit. Here is an argument for pregnant women in research not directed at conditions necessarily related to pregnancy.

Fourth, equal citizenship. To assure full moral status of individuals in society there ought to be a quality of participation in research without regard to benefit. Here the example, women of childbearing potential.

Fifth, finally, compensatory justice. Groups that have been neglected in the past ought to receive preferential treatment in setting research priorities and here the argument is women in cardiovascular research or the Women's Health Initiative.

So you see that you have multiple spheres of research taking, yes, the concepts from Belmont; yes, the justice principle is important, but making it a far more complicated understanding of justice to enable it to do some of the work that we would need to do to figure out whether justice is, indeed, sort of a key to understanding some of the important issues regarding research today.

I will stop there and we are ready to listen to questions.

DR. CHILDRESS: All right. We will give the others an opportunity as well but let me throw out a question. Given some of our discussion earlier today, how might this relate to or eliminate cognitively impaired subjects, or to use the example that Alta raised with regard to Professor Fisher's presentation, the emergency research?

Would you or Jeffrey, or Anna like to comment on that?

DR. SUGARMAN: Sure. Well, we actually -- when Alta was raising the question we scurried with notes to see if this would -- if we could, you know, take the straw dog Alta Charo test and run with it.

I think that that poses an interesting challenge to this model but I think it fits within the spheres of justice. There is certainly an equal citizenship claim in the idea of emergency research. In addition, it seems like for the beneficial types of emergency research that you get an argument there for sort of a egalitarianism kind of argument. So it does overlap and it is complicated like ethics is supposed to be. So I think it fits within that system.

I do not know. Do you want to take one of the others?

DR. KAHN: Yes, sure. Maybe to elaborate a little bit, too, on the emergency waiver example. Baruch (?) in his chapter for us uses that as one of the examples he tries to play out and makes the claim that there are the benefits of research that justice demands people ought to have access to and, as we know, the waiver has really been focused on that kind of research and in the way the policy is being developed.

He wants to balance that against protection from the harm, the risk of harm in research. So he sees that inherent tension and recognizes that that must be balanced.

The third prong that Jeremy mentioned is the social demand for the knowledge that research generates and that we need that and that needs to be balanced as well against the individual needs.

So I think we are moving towards trying to address that.

DR. CHILDRESS: Right. Does anyone want to address the cognitively impaired subjects?

DR. KAHN: Oh, we did not get to that.

DR. CHILDRESS: Before you do that let me just remind subcommittee members you need to check out by 3:00. You have an extension of time until 3:00.

DR. SUGARMAN: Well, if you march down the examples, the five notions of justice, libertarian notion of justice clearly does not fit. An individual ought to be free to accept the risks of research because they cannot make it for saying -- I guess if the person is cognitively impaired or at least decisionally incapable that they are not in a position to make a strong libertarian argument.

Individual egalitarians ought to have equal access to the benefits of equal participation. Now if you said that there were benefits that accrue to individuals by being in research and, indeed, some projects, yes, sure. So you get an argument for that, I guess, in an individual egalitarian model.

Again the group egalitarian model also accommodates the decisionally incapacitated research subjects in that individuals often bear burdens but group receive benefits. You need to recruit diverse individuals so the group would benefit. So it would fit there.

You might be able -- I do not know how it would work

under an equal citizenship model. I think I would have to think hard about that, about what you are going to call, you know, moral status and it brings us back to personhood debates and the like about moral status and being-ness that I do not want to really start on off the cuff. But I think it does in a sense find at least a home in those two.

PROF. CHARO: Can I just ask a point of clarification.

DR. CHILDRESS: Of clarification and then --

PROF. CHARO: Yes. Thanks, Alex.

Just for clarification are these models that Madison laid out for you in the book supposed to represent five distinctly different approaches to the way in which you would do a justice analysis of research or are you supposed to only go forward with things if they can somehow be justified under each of the five models so it is and, and, and? I mean how do these play into how you would actually set up? Maybe that is your question. I was just trying to clarify the role that this was playing in the book or in your analysis.

DR. SUGARMAN: I think right now we are at pretty much a descriptive stage, which giving full description to the range of problems that fall under claims about justice we can clearly do some really good descriptive work. Baruch floats the idea in his chapter about a pluralistic casuistry as the mechanism to balance these things. Madison is obviously following Walzer (?), right, spheres of justice and that idea.

So how this will pan out as we think through the next iteration of this whole book, and this book is -- it is painful to be an author and a participant in this because we are all working together to

try to move forward a bit as a group. So we do not know yet.

DR. CHILDRESS: Do you want to --

DR. KAHN: Yes. I think we can say that Madison, and even in the early draft of this and in our discussions, recognizes that I think these are more -- thinks of these as challenges to research. These are justice issues that must be addressed and thought through and, of course, there will be some interaction and overlap. They are not meant to be discreet and independent from each other at all. How that all plays out, I think, has to be resolved.

DR. CASSELL: Well, I may be hearing this because I like the idea so much. I may be hearing it this way because I like the idea but if I understand you correctly participation in research is one of the benefits of being a member of the society and I ought to be able to be allowed to participate and it is a matter of justice or injustice if I am not because I am a member of this group or that group, or this community, not merely that it benefits me directly.

But it is one of the facts of modern life that participation in research is a part of being a member of the community. I mean, that is a sort of Tom Sawyer and Huck Finn idea, you know, of painting your fences. One of the benefits of belonging in society so much so I will give you a buck to do it.

I really like that a lot. I mean, I really do. So I want to make sure that is what you are saying. Otherwise I do not understand the group -- I do not understand why equal citizenship or compensatory justice or any of those things would be involved.

DR. SUGARMAN: I think that you are right that there is a

claim towards citizenship in the research. That is what we are getting at that there is one claim towards that but that may not be overriding in every case.

DR. CASSELL: Oh, I understand. There are other reasons why I might --

DR. KAHN: That is part of what justice demands.

DR. SUGARMAN: Right.

DR. CASSELL: But given those things laid aside and not having special things or my being a special risk or something like that, all things being equal, I should have that citizenship right.

DR. KAHN: And as part of being a full citizen in the society that is part of what is expected of you. I think that is the other way as well.

DR. CASSELL: And you do understand that that is a radical difference, I think, from what anybody would have said 25 years ago.

DR. KAHN: Yes.

DR. CASSELL: You do understand that?

DR. KAHN: Sure.

DR. CASSELL: All right.

DR. SUGARMAN: But we are also trying to be responsive.

DR. CASSELL: It is on the record now.

DR. CHILDRESS: Richard McCormick's notion of social justice certainly includes some of that.

DR. KAHN: Right.

DR. SUGARMAN: Yes.

DR. CASSELL: Yes.

DR. CHILDRESS: Alex?

PROF. CAPRON: Alta was right that a concern that I was having, and I do not know if she was referring to the way I was looking puzzled, was this question of what are we talking about here? Useful categories for teasing out some ideas or criteria, or desiderata, or what is it that these various things are because they seem contradictory, they seem incomplete.

Another problem that I have with the presentation is some of the examples that were given puzzled me and it seemed to me that you have in what Baruch was saying a potential for filling in some of the ideas that you were ascribing to Madison at least by way of the examples. The difference -- it seems to me that there are at least three categories of things going on here.

One is the therapeutic orphan idea. That is to say if people in your category, however the category is conceived, women, children, pregnant women, old people, people of particular race or whatever, cannot be included in the research then the results may not apply to you and you will either be told you cannot get this drug because it is not labeled for use with you or it will be given to you and it will do you harm because your particular metabolic condition was not one of those that was studied. Now that is one meaning of it that has nothing to do with your being in the research at all but somehow people in your category are being included.

The second is the AIDS example. The only way to get access to this particular thing that is being studied is in a protocol. You

believe it is your best chance to get better. You, therefore, want to get into the study or even better than that you want to get it outside the study because you do not want to take the risk of getting the placebo but you want access to something which is still in research.

And the third is the example with the person who wants breast -- wants the bone marrow transplant for breast cancer where they are not making a claim that they want to be in a research protocol at all. They want this to be treated as accepted treatment so that their insurer will pay for it. I mean that is the way that has come up as an issue. I mean there may be women who say I want to be in a protocol but the real argument there has been this is proven enough so that you insurance company or managed care plan should pay for it and when you fail to do so you have done me an injustice because you have kept me from getting a life saving treatment.

Now those are radically different ideas and to hear them all given as examples in one way or another as having to do with the justice issues in research worries me a little. Now did I misunderstand? I mean, I thought you gave the bone marrow transplant where you were saying freedom to accept. The woman with breast cancer has perfect freedom to accept if she will find someone who will do a bone marrow transplant but that is not what her issue is. Her issue is payment for treatment. It is not a research issue at all.

DR. SUGARMAN: Well, I think we could -- that there is -- in the field there is not consensus about whether autologous bone marrow transplantation is yet an accepted therapy.

PROF. CAPRON: Oh, I agree.

DR. SUGARMAN: But that is not the point.

PROF. CAPRON: Yes.

DR. SUGARMAN: But the question is, is that it is still viewed by researchers as research, as something that is unproven, untested, and potentially harmful.

PROF. CAPRON: Yes, I agree but the woman who is asking -- it is not a question about the protocol.

DR. SUGARMAN: Right.

PROF. CAPRON: It is not -- it does not seem to me -- as I have understood it, it is the same issue as the AIDS issue which is you only have 100 people in your protocol and if I cannot be one of those 100 I have been treated unjustly. It is I am now getting treatment from Dr. Jones. Dr. Jones is willing to do a bone marrow transplant but it costs $50,000 and he is looking to the insurance company to pay for it and they say it is unproven and, therefore, it is not covered under the terms of my health plan.

MS. MASTROIANNI: Excuse me. When we were developing that example that was not the consideration. It really was an assumption of the risk, allowing the person to decide that if something is considered to be extremely risky that they can take that on themselves. They are capable of making that decision themselves.

PROF. CAPRON: Well, is that an argument that is raised?

MS. MASTROIANNI: It is a risk issue is what the focus of that particular description is.

PROF. CAPRON: But I do not understand that that is factually why the women have not been able to get it. Is that the case?

DR. SUGARMAN: Okay. So take the example. Take your example then, the libertarian one. Take the whole development of the parallel track at FDA for approved -- rapid approval of drugs that are outside the context of trial where individuals are willing to accept risks that are unproven. I mean, you know, the same agency that had to respond to thalidomide is now sort of saying, "Okay. Well, you want this thing that is experimental. It could harm you." And people who are desperately ill are saying, "I do not care. I want this. I would rather trade this versus sort of a known or unknown --"

PROF. CAPRON: It is a rejection of a paternalistic view --

DR. SUGARMAN: "-- natural history of the disease."

PROF. CAPRON: -- that an IRB or an investigator should --

DR. SUGARMAN: It is a libertarian argument.

DR. KAHN: How far should we allow liberty to push?

DR. SUGARMAN: To play versus protection.

PROF. CAPRON: Right. Which is a question really about -- not about IRBs and so forth but about the whole regulation and licensing of drugs. I mean, you could go to countries where if a pharmaceutical company can make something you can buy it.

DR. KAHN: Right.

DR. SUGARMAN: But the reality of research today is as complicated as you are making it out to be and I think I am actually -- your comments are very helpful because it challenges us further to look at these as questions of access to experimental things because there is just not enough of this stuff yet because someone did not make it from a

bark of a whatever tree.

PROF. CAPRON: Right.

DR. SUGARMAN: Versus there is something that is around a lot but it is really a payment consideration and we are worried about a different set of questions.

PROF. CAPRON: And the third versus is the one you raised just a moment ago which is we have got plenty of it and it is not a payment question. It is it is so risky that we do not think that outside some highly controlled circumstance more than ten people should be --

DR. KAHN: Exactly.

PROF. CAPRON: -- exposed to it and that is why we have Phase I and Phase II, and Phase III, and all those other considerations.

DR. KAHN: Sure, right.

PROF. CAPRON: Which, as I say, are to me bigger than IRB issues. They are the basic question of should we have regulation of drugs.

DR. KAHN: Well, we -- and we are writing this book from the perspective of all of the levels at which justice intersects with the research process. So from the policy making perspective, from the funding perspective, through the IRB, and the individual research participant's perspective as well. So --

PROF. CAPRON: That would --

DR. KAHN: -- you raise a good point.

PROF. CAPRON: That would be to me an example that would not have that other red herring of the --

DR. KAHN: Sure. Fair enough.

PROF. CAPRON: On the equal citizenship --

DR. SUGARMAN: I think we heard you on that one.

PROF. CAPRON: The chair already pointed you -- if you have not already looked at it and you may, but the illuminating exchange of views between Richard McCormick and Paul Ramsey on the question of children because that is where the equal citizenship was invoked before and the argument was if a child cannot consent but a parent looking at the child would say as a member of this community you have some reasonable obligation to take on some risks that are not just of benefit to you and I am going to consent for you and you later on as a fully developed moral person will be thankful that as part of your moral education and so forth I enrolled you and allowed you to go through that risk because that was part of being an equal citizen.

One of the arguments that was certainly raised then about the weakness of that claim is that anyone in society now is the beneficiary of all of the research and all of the sacrifices made by scientists and subjects in the past and none of us are required to now agree to be a subject because we are the beneficiaries of all of that knowledge which has been gained at considerable costs. We are only asked to pay for it in dollar terms not with our own participation.

It would require a very strong claim it seems to me to insist that indeed if you are going to line up at the drug store you first line up at the volunteer side over here and sign up to have your name randomly drawn because you are getting a drug here that somebody else helped to develop.

Unless you are willing to take that step it seems to me

that the equal citizenship argument ends up not being equal citizenship for everyone but really your obligation as a sick person to help others because it is really only a person who is sick with a disease on which research still has to be done who is really put to this, that is to say if you are going to get the benefits of this new treatment you have to participate now whereas I can go and get the drug. It is already approved. No one else has to do research on it for me to get it.

And I mean, fairly seriously, unless you are really willing to say that there really is a citizen obligation here, if you are going to participate in the society which has this cornucopia of valuable things you ought, therefore, to be at some equal risk of being drafted as it were into a research role, a subject role. Otherwise it seems to me at a very high level of rhetoric and only targets those people who are kind of stuck in the bind that research is going on, on their disease right now.

DR. SUGARMAN: Right. Or who may at some future point be stuck in that bind. It would be one model. I think the other thing is to enlarge this to research with human subjects slightly more broadly than strict biomedical research. That this may play a bigger role where people are not necessarily sick but we sort of learn about sociology research, psychology research, economic research, that there are a variety of research involving human subjects that does not fall strictly on the model. There might be a more compelling argument there. I do not know. We would have to work through that. But I know on behalf of the three of us we appreciate your vigorous questioning because we would rather hear it now than later.

DR. KAHN: Right.

DR. SUGARMAN: And it also does help in the process of our thinking through this.

DR. KAHN: Right.

DR. SUGARMAN: So we are happy to hold this straw dog up.

PROF. CAPRON: Okay. Let me understand. The compensatory justice model refers -- is a version of the therapeutic orphan argument? I mean, the fact that women were not included in the studies of cardiovascular disease would be unimportant if the findings derived from men were equally applicable to women. At that point the women would say, "This was great. We get the benefits but none of us had to be sacrificed on the altar of science to get them." The problem has not been that.

It has been all these findings maybe are kind of specific to male versions of heart disease and none of the money was being spent to find out about female versions. That is what I understood to be the argument. So it is a version -- it requires that somehow you did not get the benefits of prior research. It is not like compensatorily I should have an equal chance of being a subject.

DR. SUGARMAN: Right.

MS. MASTROIANNI: Right. Not on an individual basis.

PROF. CAPRON: Yes.

MS. MASTROIANNI: Correct.

DR. CHILDRESS: Diane and then Alta.

DR. SCOTT-JONES: I have a question about the notion of vulnerability and how it relates to the concepts of justice that you just

presented to us.

Near the beginning of your presentation you talked about some populations. As I recall you mentioned captive populations, children. You mentioned groups that we would consider vulnerable groups as opposed to generally persons who might participate in research. I was just wondering how these ideas of justice apply to the full range of experiences of participants in research who might be considered vulnerable? It seemed that what you talked about had most to do with access to research to not being excluded from research.

So I was wondering what the ideas of justice that you talked about have to do with say the treatment of children generally throughout the research process and not just in their being included in studies?

DR. SUGARMAN: I think that we in talking about this we did not select necessarily vulnerable populations. We have populations that some conceive as vulnerable populations but others, especially the people in those populations, may not conceive nor want to conceive of themselves as vulnerable. Women, persons of color, may not want to see themselves as vulnerable populations and I think that makes a lot of sense.

So we have this sort of -- these sort of categories here because those categories have been selected and there are certain paradigm cases that I think we want to find out if they raise some more questions about justice when looked at in a very tough way.

Now in terms of the treatment of people in research I think some of the models that we have or the approaches to justice very

much take into account that. The individual egalitarianism model says that there are benefits that derive to me from being in research aside from sort of the research itself.

So very much that would say how are people treated in the context of research or it recognizes that people in research are somehow treated in a nice way. They have a special research nurse or they get medical exams or there is someone who cares about them there. Someone at the other end of the phone.

That recognizes those very important parts of research that I think we have sort of missed in sort of a cold look at just the consent forms and IRBs, et cetera, the kinds of things that have been discussed for many years in literature.

Do you want to pick up on that?

MS. MASTROIANNI: One thing I wanted to say, to reiterate what Jeremy said, is that these populations were not selected because they were vulnerable.

DR. SCOTT-JONES: But why were they selected? Because you judge that they have been excluded in some way from research?

MS. MASTROIANNI: No, it is that they were raising issues -- when you read the literature, when you talk to people, these are the populations or the settings that raise concerns of justice or that we sense that there is some sort of a shift in the notion of justice. In some cases it is the straight protectionism to access. You know, this concept of protection to access. In the other populations there is more sensitivity to concerns of exploitation.

There are issues where these populations or settings may require additional protections. So it is not -- you know, it is not as if in each area we are going, okay, they used to be protected and now they want to access trials. It really is an exploration of each circumstance and as I mentioned earlier they were not selected because they were vulnerable. These are just areas that we were sensitized to through our work and reading.

DR. KAHN: Let me just add one small thing about that. I think we were sensitive to the use of the term "vulnerability" historically to those who were exploited. So it was a vulnerability of more risk being placed upon certain groups of people than others and we wanted to sort of transcend that and talk more about access to the benefits of research as well as risk of harm. So we thought that vulnerability was sort of a narrow way to focus it, too narrow for the purpose of this examination.

DR. SCOTT-JONES: Okay. But what I was actually asking you was then do your ideas apply to access and not to how persons are then treated in the research? What do you have to say from these justice perspectives that you have outlined about the treatment of participants in research beyond just access?

MS. MASTROIANNI: Beyond the initial stages of research?

DR. SCOTT-JONES: Yes.

DR. KAHN: I think we had no intention at all of focusing on merely the benefits of research. Clearly protection of individuals from the risk of research is always important, has been and continues to be. We are trying to expand the thinking about what justice demands and

can contribute to the protection -- to the respect of individual research subjects.

MS. MASTROIANNI: For example, clearly on the issue when you are talking about gender issues and the inclusion of women in research it certainly raises retention issues that people are now much more sensitive to. So in that way justice is playing itself out and how do we retain these participants? Do we have to use -- it is not just recruitment. It goes much further than that.

So there is a playing out across through the research process to the end where hopefully some benefit accrues. So there is some sensitivity to that but I really do appreciate your point because it raises it so that we can be more sensitive when we are looking at some of these other populations as well. That just happens to be a particular population that I am very familiar with working.

DR. CHILDRESS: Before I go to Alta there is nothing you have said, though, that rules out attention to other kinds of moral considerations?

DR. KAHN: No.

MS. MASTROIANNI: No.

DR. SUGARMAN: No.

DR. KAHN: Absolutely.

MS. MASTROIANNI: Certainly not.

DR. SUGARMAN: I think that the title brings it out. It is beyond consent seeking justice in research because we still acknowledge the importance of consent. We think there has been an awful lot of good work done on consent and it has still got to be there and there is nothing

to say that the other components need to be considered, beneficence.

DR. CHILDRESS: Although beyond consent is ambiguous in that regard? It might be consent beyond that would be a more accurate title.

MS. MASTROIANNI: You want to talk to Oxford about that?

(Laughter.)

DR. CHILDRESS: Jeff would never agree to that I know.

MS. MASTROIANNI: You know how they are.

DR. KAHN: It is a marketability issue.

MS. MASTROIANNI: It is a marketability issue.

(Laughter.)

PROF. CHARO: There is no justice.

(Laughter.)

PROF. CHARO: I would like to return you if I may to something you said in your preface, Jeremy, because I was really intrigued when I finally sat down and paid some serious attention to the research protocol review project or whatever the appropriate RRPP thing is.

(Laughter.)

PROF. CHARO: And the findings about the pervasiveness of trust on the part of subjects in the institutions and the investigators coupled with the personal benefit and hope documents what everybody anecdotally has been talking about.

And given that there is a growing but nonetheless small segment of the research endeavor that really does hold out the prospect

for therapy in the research context it is very difficult to dispel the hope because there is a very small percentage of protocols that really can fulfill those hopes. But more often than not that hope is misplaced because the research is simply not at a stage which that hope makes any sense. They are being recruited for the reasons that we think of as being medical experimentation.

Now as I sat back and thought about it, it struck me all over again as you mentioned here, I found myself thinking about the nature of the rules that we have and I began comparing it to the experience in contract law where the rules are written largely with the idea of arm's length transactions.

And the rules on the research endeavor are also written with the notion of arm's length transactions. The researcher gives information and then goes like this, "God forbid I should influence anybody." And then the prospective subject evaluates the information and the goal is to have all the risks spelled out and all the benefits spelled out in the most accurate way possible so that this rational actor or his or her agent can make a rational decision and then hands back the consent, at which point the experiment rolls along.

Maybe it is just unfair, or to coin a phrase unjust, to continue with an arm's length model of this transaction in light of the anecdotal experience, the group instinct, the limited, more statistically significant data that you have generated that says this is not an arm's length transaction. There may be settings in which it is.

I can tell you that when I went and volunteered to make money by being a human subject when I was in college that was

dramatically different than what you are talking about and I think there is still room for a very distinctively different setting. A set of rules governing things like Phase I, recruitment of healthy volunteers, and all other things in which people are being recruited, and all in part because they already have an illness or condition.

But with regard to that latter group it may be that all the rules need to be rethought from the point of view of saying this is not an arm's length transaction and there is a much stronger affirmative obligation on the part of the research community and much stronger constraints that can be placed.

Everybody here has heard ads recruiting subjects in which they -- and the one going on at Madison now is actually hilarious because it is about a mother talking to a daughter saying, "Have you been suffering from constipation?" And she is like, "Yes, I really have, mom." She says goes, "Well, you know they have got that new study over at UW." No, it is -- I am sorry, it was at a private lab. Thank God. It was at a private lab. And the daughter -- you know, and she goes, "Now maybe you should try that." I mean it is absolutely therapeutic in its overtones.

DR. CASSELL: That is true? You made that up.

PROF. CAPRON: No.

PROF. CHARO: No, this is absolutely true. This is an ad running. It has been running on morning radio in Madison.

PROF. CAPRON: Would the gentlewoman from Wisconsin yield for a moment?

(Laughter.)

PROF. CHARO: I yield.

PROF. CAPRON: If you want to see a print version of this, the latest Hastings Center Report has a side bar in which the person describes how to get someone to consent to research and it is -- it must be someone from Wisconsin because it is this constipation research and it starts off with a little child's voice and then a woman giving information about how you would sign up.

PROF. CHARO: I think it is a multicenter study.

PROF. CAPRON: They even had their own ad agency. But the approach is just what Alta said.

PROF. CHARO: Now --

PROF. CAPRON: I think this may be heartburn actually. It is a related study.

PROF. CHARO: That is all right. The same ad agency. But the point -- I am sorry I am taking way too long. The point simply being that we write our rules on the notion that we have got two independent rational actors and we are trying to make sure that the market can operate efficiently by making sure that you have got all the necessary information for the actors and where there is an inability for an actor to function in the market as an autonomous agent we are looking for substitute agents for that actor. Right?

We do not do it completely because we do not follow the total libertarian model here because we, in fact, do use IRBs to set an absolute ceiling on risks that we will permit. Right? We do have IRBs that say this is riskier than it need be and we are not going to let you do it even if people would consent because we can think of a way to get

exactly the same scientific value at less risk. So we do not go completely down that road but we go pretty far down that road.

And I am beginning to find myself wondering if there is a substantive component to justice that transcends its more kind of procedural aspects having to do with distribution of benefits and distribution of burdens that is at the heart of the justification in the Belmont report and all the other reports to date. Part of the justification for the absolute limitations on the risks to which people will be exposed without good reason, and this goes kind of to Baruch's value stuff, but which may also be pertinent to everything about the way in which the rules are cast and the kinds of settings in which we will permit research to go on or in which we will permit people to be recruited.

I mean, I do not know where this is going to go. This is not an organized comment but I just -- I feel like I have finally reached my limit at believing we can solve this by giving everybody enough information and enough agents, and then send them on their way, and it is probably a combination of these two people together.

DR. CHILDRESS: That is what I was going to suggest. The relational model is one possible supplement or alternative.

We will give you a chance to respond if you like to some of the range of issues that Alta raised and then we will bring this session to a close and then get Eric on --

PROF. CHARO: Or to get the address for the place for the constipation study.

DR. SUGARMAN: I did not know if you were asking for the phone number.

DR. KAHN: There is something else which you may already know about and I would mention to it if you have not seen it, and that is a study done at the University of Chicago with a very small number of Phase I chemotherapy subjects in which they are asked why they were willing to participate in this particular trial. Something like 95 percent of them gave as their first reason the hope that they would benefit therapeutically in a Phase I chemotherapy trial.

Now we know that physiologically there is something like a five percent tumor response rate in a Phase I chemotherapy trial so there is obviously a big gap there between what people hope for and what they might really expect. And that goes to exactly the point that you are raising about why people participate and what are we really doing in the research process.

A second is something that Jeremy brought up and that you brought as well, Alta, and that is the level of trust that exists between subjects and the people who do the research and the places in which the research is done. And that we ought to keep in mind because it is a ripe situation for people participating for the wrong reason.

PROF. CHARO: Jeff, just one last thing. Can you -- how does this play into the need to get consent? I mean, I am interested in the degree to which justice really is at the heart of the reason why it is unfair for some people to not be protected by rules of some sort at some level, federal, state, whatever, that say they cannot be enrolled without their knowledge of having been enrolled. They cannot be enrolled without an opportunity to say, yea or nay, and yet that is where the justice segues into the consent. I wonder if this is something you have

played with in this book.

DR. SUGARMAN: I think we have played with it a little bit before with the work of the Advisory Committee in the Subject Interview Study and in the Research Proposal Review Project, more so in the SIS, Subject Interview Study, and it may be that it would be important if your deliberations take you in this direction to either review carefully the material in the book or have one of us that was responsible for that study, or both those studies, present those to you to let you get at those data and sort of tear at them a little bit.

The data are very powerful and they do speak to some of the issues you have brought up. The data speak to at least -- and one of the differences between Chris Daugherty's work to which Jeff referred, which was only in Phase I trials, is that in the Subject Interview Study we talked to some 500 patients in a variety of different phases of research and as you might imagine the motivations for participation are different in different phases of research. There are people with different illnesses. There are different research projects. There were some that were therapeutic projects. Some were diagnostic projects. Some were epidemiologic projects.

To get at the question of consent which seems to be driving you some, some people in in-depth interviews, we spoke to 103 of them, folks who reported that they had participation in research, they said about consent that some had already made up their mind when they walked in the door. By the time they got to the physician or investigator they had made up their mind. They were going to consent to be in that project. It really did not matter what was said to them during that

consent process.

In other situations people took the consent forms home, read about them, did literature searches, and the power that these consent forms had on people was overwhelming. Several participants in that 100 pulled them out of their bags and showed them on a day unrelated to the consent visit. They were proud of their research projects.

There are data there that just really can surprise you about looking a little bit more inductively at the research process from the recruitment part to these -- now we talked to people at all stages. This was not a longitudinal study. But even the transition of reasons for participation, getting at therapeutic misconception, overcoming therapeutic misconception and the like, that might be very helpful if you go in that direction.

DR. CHILDRESS: Well, we thank you --

PROF. CAPRON: Jim?

DR. CHILDRESS: I am sorry. Yes?

PROF. CAPRON: Could I just follow up?

DR. CHILDRESS: Very briefly so we can get the --

PROF. CAPRON: Yes. No, this is not a question. This is a conclusion from this. I think we should definitely follow through on the suggestion that Jeremy just made and we should either as a subgroup or entitled as the whole group suggest that we retain somebody who understands those data to do some further analysis of them for us.

I think it is a rich field to look at and I would be very interested to know, for example, whether the investigators look at the

consent forms or interviewed the researchers who were involved in the subject process because I have been struck in years and years on the Recombinant DNA Advisory Committee how often we had to insist on the rewording of consent forms which presented what were usually Phase I studies in terms in which any reasonable person would have thought they were going to get some prospect. In other words, at most it was said we cannot guarantee that this will do any good for you.

Secondly, I would suggest that the staff, if everyone on the commission does not get the Hastings Center Report, distribute to the full commission the collection of articles in the latest January/February issue about the emergency exception in part because Jay Katz's little piece in there is a lovely in a couple hundred words reiteration of this problem rather than looking at what most people responded to the emergency -- the FDA emergency research rule as a violation of Nuremberg or something.

It looked at this basic underlying problem that arises when we too quickly treat as therapeutic things which are, in fact, research. And the fact that we do it is in my mind a big explanation of why patient subjects faced with it come away with the impression that that is what they are getting. It is not all just wishful thinking on their part.

DR. KAHN: No. It is made much worse when the investigator and the treating physician are the same person.

PROF. CAPRON: Yes.

DR. KAHN: Which is obviously a --

PROF. CAPRON: Right. And that is one of the things that

Jay and I, and others have been saying for 25 years that ought to be addressed. In a way that group is more vulnerable than normal subjects which goes against the grain that it was the normal subject who was at risk of getting injured.

So I would suggest that we distribute that. But I very much would like to see us commission one or more papers using the SIS data and getting into this because I think we really could make a contribution on that topic. It is not one that we have identified. I very much appreciate Jeremy underlining it for us.

Finally, you might also just as a way of summarizing things for people, Anna and Jeff have an article in last summer's Journal of Law Medicine Ethics, Volume 24, page 118 through 126, on remedies for human subjects of "Cold War Research: Recommendations of the Advisory Committee" that not only gives the background but some of the interagency working groups first responses and so forth.

Again it would be helpful for the commissioners to have that. So I will leave my copy if that will help you.

DR. CHILDRESS: Thank you very much, Alex.

We thank all three of you very much for joining us and sharing your thoughts with us. Thank you.

MS. MASTROIANNI: Thank you very much.

DR. SUGARMAN: Thank you.

DR. KAHN: Thank you.

DR. CHILDRESS: Time is slipping away.

Eric, would you say something about --

CHANGES IN RESEARCH

DR. CASSELL: My task has been made very much easier by Dr. Fisher's comments and by Sugarman and Mastroianni because they have, in essence, portrayed the research endeavors, the cooperative endeavor between subject. Cooperative in the sense of both being in it and not necessarily all loving each other.

In fact, when I first said that some time back it was more of a feeling that from my own observation than based on any data. Now I think there is hard data.

I think what is important, if you do not mind my doing this for just a moment, is that the basis for the model which we inherited from Belmont, and I really might say the early part of the Century, is a model of the rational human, which is a Cartesian model of how people make decisions and what science is about. Science is about truth but by rational people. Normative or emotional issues have no part in it. And when people make a rational decision or autonomous decision it is not a decision of mine. It is a decision of what any rational person in the same situation would do.

We do not live in that world anymore by any means. We do not believe for a moment that science is about some -- we may not be post modern, thank God, but we might -- we do understand -- I have a lot of bias there -- but we do understand that kind of truth, the selfless truth in which the scientist has no other interest, but truth is just nonsense. And we do understand that people make decisions based on more than intellectual values.

The question is how to have that entered into the research endeavor in such a way that people are able to participate in

the research in the way they want to and at the same time they are not taken advantage of on the one side. On the other side how to make the researcher understand that he or she is also a participant and that they have a normative obligation to protect their subjects as they do to protect science.

That this mix of problems has gotten more complicated and not less and our task, I think, is to try and lay out guidelines that will really protect human subjects for a decade or more in the future just as Belmont did that in the past.

I only mean to discuss some of these issues and put them on the table and as I say the task, I think, just got a lot easier.

Is that brief?

DR. CHILDRESS: That was very succinct. Well done.

Eric has agreed to prepare 10 or 15 pages or whatever on this. So one thing we need to do is react to this now.

DR. CASSELL: React now so it will make the task easier.

DR. CHILDRESS: Or if you want to ponder it. But if there are any reactions now it would be good to provide them.

PROF. CHARO: If you were forced to sit down and try to encapsulate a set of behaviors that investigators need to learn to engage in when they are interacting with potential subjects. Right? Do you already have a beginning image of what that would be since you are not going to limit yourself to the things that have been associated with this kind of rational act or model?

DR. CASSELL: Well, for one thing I think that the -- what we know about consent, what we just heard also, the pride in being a

part of a research project, that the investigator -- that obtaining a consent is a very important personal act. It is not an objective impersonal act. It is a personal act in which the investigator protects that subject and their own research at the same time. After all they do have an interest in what they are doing and they should be getting that consent. It should almost never be gotten by some person who has got the time. That is the way we do it now. Who has got the time? It is too important for that.

But I think that the solution starts earlier than that and I think that Celia Fisher's presentation and the discussion we had at lunch and my previous comments about education, research method is in essence -- I mean, research method cannot be separated from the ethical issues of research. When people learn research method they cannot be learning in a few hours, you know, learning something a little bit about ethics. It is essential to it. The normative aspect of science is part of science.

It is about time that a graduate of a university in the 1990s knew that there were normative elements in science and did not and could not say anymore, something that nobody with any sophistication has been saying for 30 or 40 years, that it is the pursuit of truth and truth alone. That just is -- it is silly when you hear something like that out of the mouth of an otherwise educated person and they are saying that because they do not know any better. Not because they just do not understand. They do not know.

The analogy that comes to mind is when somebody not too long ago tried to find out what do physicians know about physics.

After all it is part of their education, college education. And what they discovered was that mostly physicians know the physics taught to them by professors of physics in college who were not physicists but teachers of physics and who had learned it 20 years before. So that their physics was almost 40 years out of date. That is exactly the same thing as we have now.

PROF. CAPRON: We, of course, might want to learn more about it but there is nominally a requirement for all programs receiving federal post graduate training funds that they do some education on ethical issues and it may be a testament to how well that requirement is being carried out if the statements, the very reasonable statements you make about the inadequacy of understanding of this -- among the research population is correct.

So that would be something we ought to educate ourselves a little bit about of how that is being implemented and what kinds of things are addressed. That may be only certain of the research population, not all researchers in all fields are subject to that. I do not know. I know it is a requirement and many universities have now mounted programs for their post-docs and their graduate fellows in various fields.

DR. CASSELL: And we teach that at Cornell. I take a part of that and mine is the human subject part but it is the lesser aspect of it. Mostly it has to do with cheating in research, number one. And, number two, what to do about an imperialistic laboratory director.

(Laughter.)

DR. CHILDRESS: Another question about your

description, Eric. The changing environment of research, and we have talked in some earlier sessions about some of the changes that are occurring there, they are not reflected in what you said here because you have emphasized some other aspects but I am assuming you will focus on that as well.

DR. CASSELL: Yes.

DR. CHILDRESS: Other suggestions?

Diane?

DR. SCOTT-JONES: Eric, I have a question and a comment as well. Let me give you my comment first.

You have mentioned the importance of education and that being needed as a supplement to regulation. You might want to consider also the role of professional organizations in educating members because I know the American Psychological Association, the Society for Research and Child Development both take that approach that it is important not only to educate during training but to keep this as something that is constantly in the forefront for persons who are active in the field.

Second, I have a question. In the paper that you would develop would you move towards talking about some of the practical aspects of getting consent? For example, there are very practical things that you might move towards. Such as a procedure that involves not only signing the consent form but in some way quizzing the potential participant about what they understood of what you were saying. Will you get to the practical things that people are trying now? Because various research groups are trying innovative ways of gaining consent of

participants and I did not know if your paper was going to focus on --

DR. CASSELL: But I am a practicing physician so I feel no obligation to be practical in any other aspect of my life. But, yes, I think that. I think, in part, because the issue of what we really mean by a consent requires some of those -- some practical issues being addressed.

PROF. CHARO: The other --

DR. SCOTT-JONES: I had one more.

PROF. CHARO: I am sorry.

DR. SCOTT-JONES: And then there is also an issue in longitudinal research of revisiting the consent.

DR. CASSELL: Yes. I do mention that in here and I --

DR. SCOTT-JONES: Oh, I did not --

DR. CASSELL: Yes.

DR. SCOTT-JONES: I must have missed that. Okay.

DR. CASSELL: I mean, both the subject changes and the research changes. At the present time the statement that says, "I realize that I may discontinue my participation at any time without..." whatever it might be is the only thing that acknowledges that. But I think it has to be acknowledged.

PROF. CHARO: I am sorry. I did not understand -- I did not realize what this was when I found it on the table so I did not read it. But -- so I might be -- any chance that you might actually spend some time talking about what Alex has mentioned and others have certainly endorsed which is the idea that it is just not feasible to have physicians, treating physicians acting as PIs, as recruiters particularly, as recruiters?

Right now my impression based on a couple of meetings I have been at is that it is recognized as the best practice to separate physician from PI or physician from recruiter but it is not required practice.

To the extent that the consent process is severely undermined by the selective hearing that will follow from somebody who is exhibiting great trust which will only be greatest when you are in a therapeutic relationship it really profoundly distorts the dynamic here if we do not have a set of rules that are premised on a very protection kind of model and instead stay with us more kind of -- to appear as negotiating with one another to become partners.

DR. CASSELL: I feel very strongly about that. I gave a lecture at Sloan Kettering one time where I suggested that there was an inherent conflict of interest as all of us know. I mean that is not -- right? Oh, well, you would think that I was impugning their lineage. And I actually was but it was an intellectual lineage. But, in fact, most researchers do not see that there could be any conflict of interest. Treating researchers.

PROF. CHARO: But since, in fact, it can be approached both from the conflict of interest point of view but also from the point of view of the patient/subject simply as it is not possible to have a kind of cold rational arm's length model of a transaction in which somebody has to give an informed and voluntary consent. You cannot have that where the person who is supposed to be voluntary, independent and consenting is giving up those things because that is exactly what they want to give up in a therapeutic relationship where you want to relax into feeling like you are being taken care of.

So by talking about it from that point of view it might be a way to avoid the impugning of their character or intellectual lineage and nonetheless get the point across that this might be something we would want to consider maybe solidifying into practice instead of just exhorting on it.

DR. CASSELL: Well, it is a big problem. I mean, solving that problem is not an easy -- it is not easy because the trust is inherent. In any therapeutic relationship the trust is inherent. If you do not have trust -- I mean, the person who is unable to trust is in terrible shape.

PROF. CHARO: The solution may not be to try to destroy the trust but to try and take away some of the triggers and one of the triggers is when your treating physician is the one who recruits you. So you take away the trigger and you do not have to try to take away the trust.

DR. CASSELL: In other words, that whole business of having it, I think that is very -- maybe the treating physician should never be recruited.

PROF. CAPRON: I have a sense that we are now talking about several papers and I do not want to overburden the one that Eric is doing. I did not see much in this paper and I do not think it has to be in this paper, but it should be somewhere, about both descriptively telling us how the model has shifted, the so-called parallel track or the use of the compassion exemptions and so forth, which is that shift from protection to access that we have all talked about. And how that is affected the public perception of research? How it has affected the way in which researchers feel comfortable?

I mean, it seems to me that even if we went through all this process that we were just talking about the notion that you were separating these roles is very much based on the notion of a protection model. In other words, you want to keep people from reading the wrong thing into the process and, therefore, agreeing to something which if they were more disinterested about their situation they would not agree to. But that is only if we want to keep them out of the research or there is reasons that we want to be cautious.

Whereas if you conceive of this as the people beating on the door to get into the research they have already projected onto the research that it will be beneficial to them. What you do after that may be very much like the comments that Jeremy found and that we found years ago in being a donor for a kidney to a relative. But before the person was told any risks about being a donor they had already made up their mind.

DR. CASSELL: Yes.

PROF. CAPRON: If they were willing to go that far they were willing to sign it.

DR. CASSELL: But that changes the relationship. I mean, that changes the nature of what I -- if I am the investigator that changes what I have to do to protect my subject. I mean, if I am not --

PROF. CAPRON: I agree. And you can --

DR. CASSELL: It does not remove that obligation, it changes it.

PROF. CAPRON: Absolutely. You can address as much of this as you want in your paper. I am just saying that I do not want to

burden you with all of this if it is not required. I mean what you are talking about in some ways traces back to Franz Inglefinger's dismissal of the notion of informed consent in research because his basic view was physicians could get people to consent to anything they wanted to so talking about consent was going to be a waste of time and going through this process because you were doing window dressing only.

I also would like to see some -- so I would like to see some explicit attention to this issue of the different models and I do not think that is the way your paper is going at the moment.

DR. CASSELL: No.

PROF. CAPRON: It is not. So I just hope, Jim, that to the extent that this is down as a response to one of the topics that we identified, changes in the paradigm of research, that we recognize there are several different ones and Eric is addressing a very valuable one but we still have some need to address the other as well.

DR. SCOTT-JONES: Could I just follow up on what Alex was saying about the papers and whether there needed to be more than one?

DR. CHILDRESS: Okay.

DR. SCOTT-JONES: Eric, I like what you talked about here but I remember when you first started talking about this idea it was on this shift in research paradigms from protection to access and here you focus much more on the elements of consent which I think would be worthy of a paper but I really, really like the ideas that you talked about when you talked about the shift in paradigms and moving from the idea of protection to both protection and access to research.

So I was just wondering what exactly you would include because if you really went into all of the complexities of gaining informed consent I think that would be a huge paper.

DR. CASSELL: Well, I think I did not imply -- actually I am going to do that. That is the first thing. But in the stuff that I mentioned about consent here I am not so much interested in the act of informed consent in that way but in what does it mean when it says that I want to take part in your research? So when I say -- and that is why I say what do you mean by consent? We just heard part about that. When I say I want to take part in your research I am not saying recognizing all the possible risks and recognizing that I may not benefit from research, I am going to sign the bottom of this piece of paper. It does not mean just that. It may mean that also.

I am not specifically as interested in that as I am interested in the relationship between researcher and investigator -- a researcher and subject in the context of a changing social milieu. So I am really much more interested in it but really we are saying we are talking about the -- you know, we may not call it consent or participation. What does it mean to participate?

The consent is a legal document of assent to participation and part of that document is what I say and part of the document is what the research is. So I am not so interested in that because as we have heard and as I know from what my patients do, they have signed it before they have even read it. As a matter of fact they mostly do not read it because you could die from reading most consent forms. When you see all the risks that are listed in there, who would ever do that?

Whereas if I give somebody an aspirin they read all the terrible things that can happen from aspirin and call me up two minutes later, how could I prescribe such a terrible thing?

And I really mean to note that contrast, you know, so that is what I am about which is really, I think, the subject you are talking about.

DR. CHILDRESS: I guess it would be the case, though, that as the two paragraphs are written here actually seem to stand in some independence of the changing environment, that is to say --

DR. CASSELL: Well, they are not --

DR. CHILDRESS: But there is nothing here that reflects the changed environment. What you say here would be what you would also say for the earlier period, right?

DR. CASSELL: Yes.

DR. CHILDRESS: And so I guess the question would be whether we need to have the discussion. We need to have a paper that would do more with the changing environment and the changing paradigm.

DR. CASSELL: Actually you want to pay more attention to what it says in the title than what it says in the body.

DR. CHILDRESS: Just like a consent form, right?

DR. CASSELL: Yes, exactly right.

(Laughter.)

DR. CHILDRESS: Okay. Other comments to make about --

PROF. CAPRON: Yes.

DR. CHILDRESS: Alex?

PROF. CAPRON: I would be very interested if anyone in the research community could point us to an institution that behaves the way Alta described about the separation generally because it is one thing for us again to engage entreachment which is a familiar invocation of motherhood and apple pie about this advantage of separation.

But if there were an institution that both saw what devotion of resources would be involved in making that separation and also the feasibility of doing research. I am sure that there are some researchers who think that if they were to announce, "I am not your doctor. I am not here with the primary purpose of doing benefit. I am a scientist and this is a subject, this is an investigation of something that is intended to develop a treatment, and if there is something that comes out of this it might be a treatment for your disease but that is not why I am here. Dr. Jones, who sent you to see me, is your doctor. You should talk to Dr. Jones about your treatment. Dr. Jones will be involved."

In other words some people would think if I do that I am not going to get any subjects. I am not going to be able to do this or it is going to be harmful to the therapeutic relationship that is a good part of even research on therapy.

In other words, if we had a model where we could say someone has tried that and it turns out it was a disaster or it turns out they can still get subjects to enroll and the study still gets funded and, you know, here is what it costs, but X, Y, Z institution is doing that, or even a subpart of the institution. In other words, if we had some concrete real world experience to relay to the research community about

this rather than just once again saying it would be better if you would do this or you are going to have to do this.

DR. CHILDRESS: A very good point. And let me just see, does anyone on the subcommittee or anyone in the audience know of a model we could refer to?

DR. FISHER: I can mention something. It might be a little different than what you are talking about. But some of the people that I interviewed and some things I have recommended is a participant advocate who actually approaches the potential participant prior to the individual that is doing the recruitment and at that point determines not only the competence to consent but whether or not there is this potential for coercion. So that is one model that has been tried.

The other model that is very interesting, it is an EMBER (?) study published in 1986 in the American Psychologist which is referenced in the case book that also addresses another issue of conflict of interest, is what happens when you are doing a treatment protocol and the particular research subject is not improving? Who makes the decision to withdraw that participant from the trials? And what EMBER in the NIMH depression studies did and what they did was they brought in an independent clinician who when the primary researcher and treatment person disagreed or when it was the same person the independent treatment person was brought in to make that type of decision.

So there are written models of how those kinds of things are approached.

PROF. CAPRON: And in terms of the other, why don't we

just draw up a short announcement and put it in IRB, the Hastings Center Report, other journals, in Clinical Research, in the American Psychologist or something asking people if they are familiar with studies that were conducted on this or even better, who institutions that have tried to model themselves so we can get some data to share even if it is --

DR. CHILDRESS: Would you mind writing that up?

PROF. CAPRON: Why don't they just take the transcript.

PROF. CHARO: Yes, I think you are looking for institutions. I mean, I think all of us could give you studies in which the physicians have had somebody else doing the recruiting. That is --

DR. CASSELL: Well, this --

PROF. CHARO: Or if you have never even heard of that actually being done, I can give you studies that have done that.

PROF. CAPRON: Oh, no, I personally --

PROF. CHARO: You are looking for --

PROF. CAPRON: -- I have heard of that.

PROF. CHARO: -- whole institutions that have adopted it as a policy.

PROF. CAPRON: I was referring to the whole institution. If somebody said we believe in this so firmly.

DR. CHILDRESS: Let's get Bill in.

DR. FRIEDMAN: Just a comment. The Indian Health Service is not that institution but the reason it is not is it is in part. When we review -- the IRB reviews research that is done that we are involved with even though we are not the PI or something. So, for

instance, the Women's Health Initiative. And on that one in particular but on many we want of the person doing the consent and interacting with the person to be other than the person's primary provider.

But I realize from the discussion and the reason I wanted to sit and tell you this is that that is only part of the problem. From what you are saying it is also what happens after the consent is obtained that is -- there is still a problem about the projected -- about that therapeutic relationship versus the research relationship so that I just realized the Indian Health Service does not go far enough if that is what we want to do.

You might want to separate out those two points and say you want both of them.

PROF. CAPRON: Yes.

DR. FRIEDMAN: It is not just how consent is obtained but then that whole relationship afterwards while you are on the trial.

PROF. CAPRON: Right. No, I agree.

DR. CHILDRESS: Thanks. So you will pursue that?

PROF. CAPRON: Yes.

DR. CHILDRESS: Great.

Okay. Anything else for Eric? We do have the recommendation of what we are pursuing right now but also maybe doing more on the changing nature of research and research paradigms even though this may be part of what Eric will do. We may need a full report on that as well.

Okay. Anything else for Eric?

(No response.)

COMMUNITY

DR. CHILDRESS: You also have at your -- before you somewhere in the stack of materials something I drew up on community and possible directions for a paper on community and research involving human subjects. This is just a sketch that pulls together some of the things we talked about earlier.

And it seems to me that one thing we would want to do is see whether this direction or these directions are useful and also how to develop them further. What kinds of additions you would like to make to this. And then also throw out some names either now or give them to me over E-mail of possible people that we might get involved.

PROF. CAPRON: Well, Jim, if you would accept one comment now.

DR. CHILDRESS: Sure.

PROF. CAPRON: When we talked about this briefly before you acknowledged that there were many different meanings of community, a family of concepts or whatever that were going under the same name, and I wondered whether you were suggesting -- whether you meant to suggest as you did in saying here is an outline of a paper or something, here is a precis or paper that we would again have one paper that would look at all of these or several different papers.

And I, in particular, would underline the difference between arguments about an individual approach to ethics versus a communitarian approach as one topic versus the recognition that the individuals who participate in a research project or in a consent process are themselves not isolated individuals but are the products of their

communities, and their families, and their ethnic background, and a million other influences. So they are not atomistic. I mean that is -- that seems to me a different use of the notion of community.

Were you saying that those would all be dealt with in this paper?

DR. CHILDRESS: It seems to me that I am not sure that it is worth having a paper that would simply pull out one of these. It seems to me what we would really want is someone who would sort these things out and indicate the different kinds of community that go on in the context of discussion. That it seems to me is what would be most useful for us is to, in fact, have it all together but analyze and sort it out in a way that can help us get a sense of it.

PROF. CAPRON: Okay. You are a better judge of the feasibility of --

DR. CHILDRESS: Well, at least it seems to me that if we can find the right person that would be the sort of thing that would be the most useful to us.

PROF. CHARO: Do you think somebody like Martha Nussbaum or Mary Anne Glendon might be able to do that? I do not know that they focused on the research context but they have run through a lot of other topics and looked at the kind of differing implications of communitarian models and more typically U.S. models.

DR. CASSELL: I think Martha Nussbaum is --

DR. CHILDRESS: Other suggestions?

DR. BRITO: Not to minimize the issue of community but is it possible just to include the discussion of community, instead of in a

separate paper, within the context of what we just discussed vulnerability, justice -- we have not defined how we are going to discuss vulnerability but justice and/or vulnerability and just discuss how it is going to apply to individual relationships?

DR. CHILDRESS: Well, part of what we are doing here it seems to me is we are doing the background work so that we will have some better idea of what is involved when we come to prepare our final document.

So it is not as though we will be incorporating this whole paper in our final document rather this would help us understand what is going on and why it is important to raise it as Zeke Emanuel did at our first meeting the overlooked notion of community and bioethics. It was unclear there whether he was offering it as an alternative to -- that is or in addition to the principles we already have in Belmont or whether it is simply another way to interpret those principles.

What I tried to do in the part that Alex was referring to is showing how one might use the lens of community as a way to reinterpret the Belmont principles like respect for persons and justice as a form of participation in relevant communities and the like.

PROF. CHARO: Jim, could I also suggest that perhaps Zeke and Larry Miike be polled by E-mail to comment on this and to add other examples that they might have had in mind when they were talking during the first meeting?

DR. CHILDRESS: Larry, also. Yes. Thank you.

Okay. Other changes you would suggest?

This is a very good suggestion to get both Larry and Zeke

involved in the description.

DR. SCOTT-JONES: I think it would be good to make sure that whoever writes the paper would enrich the ideas with examples. For example, to use examples of communities taking part in the design and implementation of research protocols so that they are not merely ideals but whoever writes the paper would show us the instances in which this has been done or attempted.

PROF. CHARO: I think Laurie Flynn probably would endorse the notion of concrete examples, too, of situations in which recruitment or enrollment would be premised upon involvement of family members and certain kinds of situations involving certain kinds of subjects. Not only in children as it is done now but she would point to the cognitively impaired as she talked about the effect of their enrollment and their changing symptomology on family members who may have had no ability to control what the events were going to be. She might want to have somebody take a closer look at the implications of that and the acceptability of it under current regimes.

DR. CASSELL: Alta, wouldn't that also have --

PARTICIPANT: Would you use your microphone, please?

DR. CASSELL: Wouldn't they also have --

PROF. CHARO: Would you attach your microphone to your bow tie, please?

DR. CASSELL: Yes.

(Laughter.)

DR. CASSELL: -- groups like the -- of similar individuals. I am trying to think of the name of it and I cannot think of the name.

Not like a therapeutic community but like a community of like. For example, in Kansas City the mentally retarded run their own help line and so that community has formed a community so when things like participation in research start in that community they spread through the whole community in no time at all. It is not just the AIDS group that have done that but this also. So that -- and there are many, many communities like that in the United States.

DR. CHILDRESS: Other thoughts?

PROF. CAPRON: I was just going to respond to something that Diane said quite correctly before which --

PARTICIPANT: Would you use your microphone?

PROF. CAPRON: -- inadequately labeled piece of paper and that is that thing that says "National Bioethics Advisory Commission Projects-1997" is simply my attempt to put down on a piece of paper --

PROF. CHARO: That is from you.

PROF. CAPRON: -- the topics that I have gathered we had talked about in the past and we did not have any kind of an outline of our work and I just as a volunteer put that together. I did not want to stick my own name on it because it seemed to me it was really just a reflection.

DR. CHILDRESS: It was a community project.

PROF. CAPRON: It was a community project as it were.

DR. CHILDRESS: But it is very helpful to have it and this was the next item I wanted to turn to.

PROF. CAPRON: Well, I am about to depart which is why I mentioned it.

DR. SCOTT-JONES: I am, too.

PROF. CAPRON: The one thing about it, Jim, is that the discussion of the last day has simply enlarged the number of things that are on that list and I think underline the need both to prioritize our work and to realize that we are talking about some multiyear studies here.

DR. CHILDRESS: Yes.

PROF. CAPRON: And the higher ups ought to be very aware that there is a lot of valuable work to be done that is not going to be done by October 1st.

DR. SCOTT-JONES: I have to leave also and I think that it would be useful, Jim, if in some way we could convey to you or either share over E-mail our thinking about anything that we have not had the chance to discuss here adequately about what papers we would want to go ahead and commission. Could we agree to do that?

DISCUSSION OF PLANS FOR NEXT MEETING AND BEYOND

DR. CHILDRESS: Please do.

We really need to do that and also to talk a bit about -- I am not sure how the next meeting is being conceived. Whether, for example, there will be time for a subcommittee meeting on the 13th and 14th. But something where inviting people into the group for the group as a whole. I would very much like to see Ruth Faden join us and talk a bit about her work as chair of the advisory committee and the kinds of recommendations that have come out of that group for NBAC.

Also if groups are being invited we have talked about having investigators and researchers and some from industry and also perhaps some patient groups, but whether we will bring -- whether we

bring those in it is not clear. But at any rate we have talked about having all three appear before us at some point.

We have -- people are getting ready to leave but there are a couple of other things we need to do before turning to public comments.

One of them is, Alta, this -- let's talk about it. It may be with people departing too late to --

PROF. CHARO: It may be too late to do it. Can you pass me my copy? I gave you my own copy by accident.

DR. CHILDRESS: -- at least have a discussion at the next meeting.

PROF. CHARO: Yes. What I prepared here was what I hoped would be a no brainer. Following the last full commission meeting it struck me that the clear consensus of the group was that there ought to be coverage of every person in the United States who might be enrolled as a human subject, coverage by some set of protections.

And without endorsing any particular set of protections, without endorsing the Glenn bill, without endorsing federal versus state or anything like that, what I have tried to prepare here was simply a draft of a memo that could form the basis for a motion and a recommendation to the full commission that the commission make a statement endorsing the idea that there ought to be universal minimum protections for human subjects in the United States regardless of the source of the funding of the research and regardless of the topic of the research.

To walk you through it while you are reading it, basically

all it does is repeat the statements that we have heard here from OPRR staff, for example, on the kinds of incidents that they are aware of that document the existence of noncovered research, the fact that that noncovered research has had effects that range from physical to financial to dignitary.

It notes that the Belmont report's concepts of justice do not merely limit themselves to fair distribution of benefits and burdens but implicate the idea of a reduction of risk in and of itself and that that in turn is closely linked to basic protections that allow people to protect themselves as part of the overall reduction of risk and experimentation so that there is a kind of justice based and Belmont based support for the notion that there ought to be universal protection.

And, finally, notes that 25 years ago the Tuskegee report called specifically for such a thing and added one other thing which I did not even include in the recommendation because the Tuskegee report 25 years ago said, "Congress should establish a permanent body with the authority to regulate at least all federally supported research involving human subjects whether conducted in an extramural or intramural settings, or sponsored...ideally the authority of this body should extend to all research activities even those not federally supported."

So they were asking for a permanent body that would have the kind of authority that OPRR cannot have now because it sits under a department secretary.

What I was proposing is that we recommend to the full commission that NBAC endorse the policy first recommended by the Tuskegee panel and call for appropriate federal or state action to ensure

that no person in the U.S. is the subject of research without the protections of informed consent and IRB style peer review as exemplified in the Federal Common Rule. I used the word "exemplified" quite deliberately so that it did not call for adoption of the Federal Rule because of some technicalities there.

I was hoping it would be easy but I am not sure that it is an easy thing to agree to recommend to the full commission.

DR. CHILDRESS: Any response?

DR. CASSELL: It would be hard to argue against it.

DR. CHILDRESS: That is understood as an ethical ideal rather than a specific set of regulations.

PROF. CHARO: Right. To be fair, Alex Capron would object if he were here and say this is mom and apple pie, and Pollyanish and says nothing and does nothing, and you should be aware that he will probably say that. I do not know that he would vote against it but he might say that because he said it last night at dinner.

DR. CASSELL: So go the next step and tell us how.

PROF. CHARO: Tell us how what?

DR. CASSELL: How to make it policy.

PROF. CHARO: I think how to make it policy is -- oh, the Glenn bill is one attempt to do exactly that. I do not want to jump the gun and talk about specific legislation. I would love personally no matter how Pollyanish for purely symbolic value to see our commission recommend -- you know, recommend to the President that every human being should be protected at least to some basic extent regardless of how symbolic only that is. I think it is not -- at worst it is not harm/no

foul.

DR. CASSELL: I do not think that is Pollyanish.

DR. CHILDRESS: No, I think it has a whole lot to commend it as a statement of ethical ideal. Why don't we -- people look over this carefully? Why don't we -- and see if we can get some time at the beginning of the 13th and 14th meeting to see whether we agree as I think most of us do and submit it with whatever further changes you might like to NBAC.

PROF. CHARO: So that we -- but we will not be meeting as a subcommittee so you are talking about informally doing this or are you talking about formally doing it during the main committee meeting -- commission meeting?

DR. CHILDRESS: Or doing it during the --

PROF. CHARO: Sure.

DR. CHILDRESS: At the beginning of the meeting and present it and have a chance to --

PROF. CHARO: Exactly. And I apologize that I, too, got everything in at the very last minute.

DR. CHILDRESS: Right.

PROF. CHARO: I have joined the club.

DR. CHILDRESS: Thanks very much for doing this.

Any further response to this?

Anything else we need to talk about before we get public comments?

I think there are two people. Two people who are planning to make public comment.

DR. BRITO: Clarification on the issue with vulnerability and Celia Fisher's presentation. Diane and I will be communicating with each other through E-mail. Where are we with that? Should we be --

DR. CHILDRESS: I take it you are going to be drawing up a kind of description along the lines of what Eric did and what I did on community.

DR. BRITO: Okay. For the next meeting.

DR. CHILDRESS: Well, maybe circulate it on E-mail and go ahead and get some responses and see if we can find someone that can get a paper, or you and Diane will do it, or do it in relation with Professor Fisher, or whatever you want to do on that. But I think go ahead and get the draft ready.

DR. BRITO: Okay.

DR. CHILDRESS: Okay. Anything else before we get public comment?

(No response.)

* * * * *

E V E N I N G S E S S I O N

PUBLIC COMMENT

DR. CHILDRESS: Okay. I have two people who are listed, a James Shelton and Susan Rose.

Mr. Shelton, would you identify yourself? You are with USAID, right?

MR. SHELTON: Sure. I am Jim Shelton with USAID and this is really in follow-up to the discussion, I guess, before lunch about the various federal agencies and the Common Rule. I guess Mr. Capron described it, perhaps there were certain operators that were inside these agencies and perhaps I might be described as an operator within my agency in terms of kind of implementation and so forth.

So I just wanted to -- I just did not want to pass up an opportunity. I know there is going to be this interaction and so forth but just to say -- give you a flavor of kind of my perspective on this having worked on the Interagency Committee for almost 20 years.

The first is from my perspective I think the Common Rule has actually worked remarkably well. I think it makes a lot of sense to be sort of looking at the problems with it. But I think the glass is at least half full as well and that if you sort of -- if you think about all the IRBs and all the studies and all the research that is going on with federal funds around the country, I think that is a point not to lose.

But I also think part of the reason that it works well and AID has adopted it and is implementing it is one of the points that Dr. Cassell actually made which is that it is not just the regulatory aspect that is making this thing work. I would submit that there is actually sort

of a social norm phenomenon that has taken place that people's -- there is a legitimacy that comes from the federal government, et cetera, et cetera, that spills over and there is education that goes on. I think you are quite right to focus not just on regulation but to focus on other aspects that might improve protection.

Having said I think the Common Rule is working well, I do think it needs a new look and one prism that I think you folks ought to be aware of in terms of looking at it is the National Performance Review and recognizing what is actually going on in federal government. We have been tasked with the task of doing more with less, lots more with somewhat less, and some agencies actually are downsizing and so forth, and federal agency has been mandated to reduce its process, its regulations by 50 percent. So again this issue of regulation and how to apply it I think is pretty important.

From where I sit there is a fair amount of process in what we are talking about and, you know, I think where I sit in government I see a lot of process. I really do feel that unnecessary marginal process is really very detrimental to important work and, you know, it is really part of my mission as I see it to try to ask the question is this process really necessary that we are talking about here. Is someone signing this piece of paper? Does that really add value to every single thing that happens in government? I think you really need to think about that.

The reason I think it is especially important in this context is I have a real sense that there is a lot of processes going on. Some of which may not have a whole lot of yield and that the way to come at this is to prioritize a lot better. To really try to figure out ways

to focus on the things that are really of concern and most concern to people and not spend so much effort especially on regulation if you will on the things that may not be so problematic. I think it is great that there is going to be some gathering of actual data on this information but I think that principle is really pretty important if we are going to try to do more with less.

The other point is that I really think we need to be a lot more clear -- a lot clearer in the Common Rule. There are ways that the Common Rule is not as clear as it could be. And I guess I will get to that in specifics.

My main concern about the Common Rule specifically is that it really arises from a biomedical, experimental, indeed therapeutic paradigm. That is where this thing comes from and just listening to you folks talking today that is 95 percent of what is being talked about or maybe more, and that is sort of the model.

My concern is that that is not really necessarily the best paradigm for what the Common Rule can potentially be applied to because remember Mr. Capron said, "The definition is actually very broad and to some extent very ambiguous." It has not tended to be interpreted that way.

This by the way is one of my concerns about the Glenn bill, is that I think we need to be careful about what we are talking about. I mean, anything that is sort of systematic and for generalizable knowledge, unless it meets some exception falls into this category and that is a lot of things.

Within the arena that we usually talk about I am

especially concerned about social science and I am grateful to Alta to raising the issue of survey research. I think we need to look at that a little bit more and I think we ought to comment on social science research a bit differently and think of it in a different paradigm.

In addition to survey research there is all kinds of other stuff, cultural anthropology, operations research, epidemiological outbreak investigations, market research, and also the point about evaluation research that was -- or the issue of trying to improve quality.

I mean, in the world that I live in everybody is enlightened and trying to get to serve the customer better. You know, we support a lot of private voluntary organizations, CARE, Red Cross, Catholic Relief Services, you name it. We want them to be communicating with the customer.

And if we put up obstacles in the way like you have to get a Human Subject Committee approval if you want to communicate with your customer then there are some problems with that. So I think it is not just them. There are thousands of entrepreneurs and people in the developing world that we want to encourage this kind of behavior from and we want to make sure that we are, you know, regulating this in a proper way.

Just to extend it completely absurdly almost, one could almost construe these proceedings as a human subjects research effort. I mean there might be an exception because of the public official exception but I am not sure everybody that was here today was a public official. You know, it is systematic. You are trying to get generalizable knowledge.

We are human beings and, you know, somebody's reputation could be at stake. I mean, this is -- this may sound absurd to you but the fact is the definition really in my view needs to be tightened up significantly. I mean, it could apply to criminal investigations. It could apply to congressional investigations in a sense. I have beat that horse enough.

Again I think there should be a relook at social science and to sort of come back with what are we really concerned about here and sort of look at that again.

I really liked the discussion in the context of cognitively impaired if that is going -- of different levels of risk. I mean, I think one way to get out of this box of the process is if there is some way that we can sort of mutually agree on what really is important risk. We have minimal risk, whatever it was, more risk and more than that. I forget what the categories were. If there were a way that we could do that and really focus on the things that are the most important and vulnerable groups and what have you. I really think there would be a lot more benefit and a lot less problem with it.

So anyway I think there ought to be ways to creatively think of categories of research. You know, maybe some things do not even need to go to an IRB prospectively. They can just be subject to retrospective review or something as to some extent some things are already. Or maybe classes of research can be sort of put in a certain category if you will. I just think that some things need a lot more time and attention and some things do not.

If you want this to be really a win-win-win situation I think

you have to sort of balance these things. Thank you.

DR. CHILDRESS: Thank you.

PROF. CHARO: Just by way of full disclosure, this is one of my old bosses.

Jim, I want to understand what it is that you would like to see as an outcome because survey research that does not involve identification of the subjects or observational research already is exempt and you already have procedures at AID that allow the cognizant technical officer to make that judgment call and say no IRB is necessary.

When you have a survey that involves interactions that are identifiable there is already a mechanism in place by which ranges of risk are anticipated and, indeed, things that are minimal risk can get the kind of expedited -- there is an expedited review procedure and most surveys fall in that category but there is a look at whether or not the survey does involve a risk that is greater because of, for example, some kind of sensitive subject matter which can easily happen in the context of sexually transmitted disease, reproduction, a variety of things. All of which, in fact, in the report on behalf of your agency you acknowledge.

So what would be the difference between a social science model and the model that is in place that specifically you think would be of service in the way in which, for example, your agency operates where it does a lot of survey research?

DR. SHELTON: Well, I guess I have a couple of concerns. First of all, we worked very hard at trying to fit square pegs into rhombus holes in a sense if you will. We had to -- in fact, there was latitude in the Common Rule to do that. Agencies can do that. It is, you know -- it is

subject to the interpretation of the agency. But things -- to make sense because I think partly because things like operations research were never sort of seriously considered in the context of the Common Rule, at least the predecessor HHS rule on -- or HEW rule on the Common Rule, which is about 99 percent the same thing.

I am worried about institutions that do not have IRBs that might want to do survey research. I am worried about --

PROF. CHARO: So the problem is --

DR. SHELTON: -- that not every agency, you know, will, you know, interpret these things. I think if you want to avoid process you come up with clear guidelines to the extent that you have and then you let people --

PROF. CHARO: Right.

DR. SHELTON: -- you know, have freedom to adjust within them. I am not sure -- you know, Mr. Capron mentioned HUD. You know, I do not know if HUD has gone through this process or what have you in terms of these kinds of things but I think there can be classes of research that any sort of reasonable body of folks can kind of come up with to say, "Well, these belong here, these belong here, these belong here."

PROF. CHARO: But what I am talking --

DR. SHELTON: And then not have to go through the process, et cetera.

PROF. CHARO: Well, what I am trying to point out is that to some extent that has been done and, in fact, that is your own procedure already.

DR. SHELTON: It is my procedure but I am just one agency.

PROF. CHARO: No. It is the procedure -- all of them. I mean, to the extent that they adopt the Common Rule that they --

DR. SHELTON: I think most agencies have not really thought about survey research and they have not thought about social science research, and they have not thought about programmatic research.

PROF. CHARO: Well, I think that is probably true. I think a lot of agencies adopted the Common Rule and then never noticed that they did. HUD being a prime example based on their letter.

DR. SHELTON: I would be reasonably -- I am reasonably sure that Senator Glenn has not thought about the fact that perhaps congressional investigations might be subject to -- again to this rule.

PROF. CHARO: So are you -- I am just trying to get -- I am just trying to understand what your bottom line is. Is your bottom line that you would like much greater clarity over what is covered as research and what is not, that that is the real crux of the difficulty for you at the moment is operations research, service delivery, evaluations, congressional investigations and participation in --

DR. SHELTON: I would like to see --

PROF. CHARO: -- all things where you feel like it is a pain that you have got to even worry about who is going to make the decision of whether or not it is exempt.

DR. SHELTON: I think not just me but I think the government. I think congressional investigations ought to be excluded. I

think it ought to be clear enough so that we know that. I think that certain classes of social science research should be treated differently. I think informed consent as in the sort of -- we have been discussing it today can be a significant problem with certain types of social science research and the paradigm should not necessarily be the same.

PROF. CHARO: Right.

DR. SHELTON: So I think there are different -- it is not -- what I am saying is I do not think the one size fits all approach works very well.

PROF. CHARO: But I am just trying to understand what it is that you are proposing.

DR. SHELTON: I understand.

PROF. CHARO: One easy cut off would be anything that involves touching somebody's body goes in one box and anything that does not goes in another.

DR. SHELTON: Oh.

PROF. CHARO: And that would be a way to get at invasive and it would certainly incorporate most biomedical. Now there would be some very touchy noninvasive survey or other kinds of participatory anthropological research. So you would have a new set of procedures for these nonphysical research areas?

DR. SHELTON: Yes. I mean, I think if the starting point were experimental biomedical, maybe therapeutic, maybe not, research and invasive procedures, if that were the starting point, you know, I think you would get 98 percent of what we are really concerned about just with that definition. In other words, instead of starting with the definition of

just everything --

PROF. CHARO: Right. But then we would not know what the hell biomedical research is. I mean, all of the stuff that AID does on service delivery, on family planning, contraceptive things where they are talking about attitudes and acceptability would fall exactly on that horribly fuzzy line now. So I am not sure --

DR. SHELTON: Well, I think --

PROF. CHARO: -- that it helps.

DR. SHELTON: No, I am saying we start with a well-defined 98 percent and then maybe we think about some categories that capture what you are calling the fuzzy line and some things would not be worth dealing with and some things would be worth dealing with but I would say in some other kind of way. I mean, most are pretty low risk kinds of things.

DR. CHILDRESS: But then risk is introduced as a factor, not simply touching.

DR. SHELTON: Yes. I think -- of course, that is --

PROF. CHARO: Right. I am still trying to figure out what the --

DR. SHELTON: -- sure, I think --

PROF. CHARO: -- other way is. Right.

DR. SHELTON: The risk comes from -- presumably from that but maybe not --

DR. CHILDRESS: No, it does not.

DR. SHELTON: -- not just --

DR. CHILDRESS: A survey where I am identified can put

me at a severe risk of psychosocial harm.

PROF. CHARO: A survey where I am identified could put me at a risk of beaten up or beaten to death by my husband in the United States. So what I am trying to get at is assume that we were going to say survey research as a class is on average lower risk than the invasive biomedical research. No problem there. Some survey research does pose significant risks. No problem or disagreement there.

You are suggesting perhaps we would want a different set of procedures for survey research than we do for biomedical in light of this different distribution of the frequency of risk.

DR. SHELTON: Right.

PROF. CHARO: But what is it that you are suggesting that would be different from the way we go about sorting biomedical research protocols into their levels of risk and reviewing them? What would be different about the way you will do it with surveys that will still protect the people at the -- who are going to be involved in the high risk surveys?

DR. CHILDRESS: This will be the last response.

DR. SHELTON: Okay. I think biomedical research ought to be tiered.

PROF. CHARO: It is.

DR. SHELTON: Well, it is slightly. It is not very well -- it is not that tiered in my view. I think it would be more tiered. You talked about the matrix.

I think that -- and I think survey research can be better tiered than it is now without going into more detail on it. I think that,

you know, we can talk about it after or something like that.

Just to give you an example, this business of identification, a lot of surveys people are identified just so that the supervisor can come potentially and check up on the -- but beyond that they are not identified at all. So if we -- you know, but the fact is technically they are identified for some period of time. So if we could sort of deal with that category again -- which is very common survey procedure in my experience, very, very common. That would sort of mitigate a whole set of activities in my view and help us get at the really risky ones.

DR. CHILDRESS: Thank you very much.

Okay. Ms. Susan Rose, Department of Energy?

MS. ROSE: In a gesture of kindness I am going to save time.

DR. CHILDRESS: Anyone else from the public wish to speak?

(No response.)

DR. CHILDRESS: Okay. Well, we thank all of you for your patience today.

Subcommittee members, thank you for yours, and staff.

We have a lot to communicate over E-mail getting some people lined up.

(Whereupon, at 4:15 p.m., the proceedings were adjourned.)

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