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OF THE

NATIONAL BIOETHICS ADVISORY COMMISSION

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REPORT TO THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH FROM THE OFFICE FOR PROTECTION FROM RESEARCH RISKS REVIEW PANEL 115

P R O C E E D I N G S

FEDERAL OVERSIGHT ACTIVITIES

PRESENTATIONS FROM AGENCIES

PROF. CHARO: First of all, I would like to thank all of you for coming and to extend the apologies of the chair. Dr. Shapiro is speaking at a meeting of psychiatrists elsewhere in Washington on the topic of our most recently released report on research with persons impaired capacity for decision making. He expects to be here in approximately an hour to an hour-and-a-half and he is very sorry that he was unable to be here as well as there.

We are going to be hearing this morning from a number of people from federal agencies that conduct or support research and we have asked everybody to limit their comments to five minutes. I apologize for the very short time for presentation but it is in an attempt to leave some time for real conversation. We have asked everybody to sit at the table specifically so that the conversation can range across all agencies at the same time.

At Dr. Shapiro's suggestion, we are going to have the presentations done one after another and leave discussion for the end so that issues that cut across multiple presentations can be addressed with the same

question.

I have asked Dr. Meslin to simply, you know, raise a little card that says five minutes as you are speaking so that you will know when you have reached that and you might want to think about trying to wind up if you ran longer than you expected. This is not an attempt to be obnoxious but just with 12 people to present even at five minutes a piece it will run us an hour just to get through the presentations. I think we will all be grateful for the time limits by the end.

Judging by how hearty people look at the end of that, we will either take a short coffee and respite break immediately after that discussion or move right along.

The first person who will be with us today to speak is Dr. Marjorie Speers, who is substituting for Dr. Dixie Snider from the Centers for Disease Control and Prevention.

Good morning.

DR. MARJORIE SPEERS

CENTERS FOR DISEASE CONTROL AND PREVENTION

DR. SPEERS: Thank you

Thank you for the opportunity to provide testimony to the commission on the implementation of the Federal Regulations to Protect Human Research Subjects.

At the October 2nd meeting of commissioners and federal agencies I raised numerous issues and made several recommendations for improving the federal human subjects protection system.

Today I will make only a few points and suggestions for improving the current system because I believe that the important role that the commission can play is to identify ways to improve the system.

PROF. CHARO: Excuse me, Dr. Speers. If I could just ask you to pull the microphone a little closer.

DR. SPEERS: Is that better?

PROF. CHARO: Yes. Thank you.

DR. SPEERS: There is a tremendous need for leadership, guidance and education. An office that can serve as a focal point for all the federal agencies that are signatories should be established. The role of such an office would be facilitative and may or may not be regulatory.

The federal regulations were written essentially 25 years ago when the primary focus was on providing protections to individuals who participated in clinical research and to some extent in behavioral research. Research was generally conducted by a single investigator in a single university.

In the past couple of decades there have been significant changes in the way research is conducted. Many different types of research are conducted, each with unique ethical issues and human subject protection needs. The federal regulations need to be examined and accordingly revised or interpreted to provide the protections that are needed in the current context.

Education is paramount to protecting human subjects. Our current system is based on investigators and institutional review boards being fully informed about the ethical principles and regulations for conducting research ethically.

A sustained wide-spread educational program is needed to heighten understanding and for consistency across federal agencies in the implementation of the federal requirements across IRB's and by investigators.

Two, we need to acknowledge that different types of research are conducted by various agencies. In particular, CDC is interested in the commission examining the ethical issues and conducting population based or public health research where the community is the subject.

The federal regulations were written from the perspective that individuals participate in research. While some public health research targets the individual,

other research does not. In fact, the commission already encountered this issue in its deliberations about genetic research where family members can be influenced by the research.

Another example is in community intervention research where interventions are delivered to many members in a community and investigators do not work with or know individuals as subjects. Community intervention research entails many different types of interventions from behavioral or educational interventions to the releasing of materials into the environment. Community intervention research poses many ethical challenges, not the least of which is related to informed consent.

At present, we are forced to fit this type of research into the current regulatory structure. In some cases, some of the requirements seem to be overkill adding no real protections to the human subjects. In other cases, additional protections may be needed, which are not required under the regulations and, therefore,are lacking.

The third point: Attention should be given to research involving little or no risk. The appropriate handling of this research may not be to exempt it from IRB review. However, reviewing it under the current regulation seems excessive. Survey research,

particularly of large population samples, is a good example. In large surveys, the most likely harm is from a breach in confidentiality yet the same requirements regarding informed consent and documentation of consent apply. The current two level of risk system of minimal risk and more than minimal risk may not be sufficient.

Thank you.

PROF. CHARO: Thank you very much.

Dr. Edward Lane? Has he arrived? Is he not coming?

Mr. Roger Cortesi from EPA?

Hi?

ROGER CORTESI

ENVIRONMENTAL PROTECTION AGENCY

MR. CORTESI: We do not do very much -- unaccustomed, as I am, to public speaking I disconnected the microphone.

We do not very much research involving human subjects and the risk is very low in all cases and I hate to say we find that the current common rule for us works very well.

PROF. CHARO: Thank you. You have gained us at least four minutes.

(Laughter.)

PROF. CHARO: We will be back to you in the

discussion, though.

Dr. Lana Skirboll from NIH.

DR. LANA SKIRBOLL

NATIONAL INSTITUTES OF HEALTH

DR. SKIRBOLL: Thank you for the opportunity to be here today. The NIH, I think everyone knows and I think we articulate it in many fora, is committed to protecting the rights and welfares of those who elect to participate in research. Individuals who participate in NIH supported research have been afforded the twin protections of informed consent and independent review by local IRB's for more than 25 years.

The core DHHS Human Subjects Protection, otherwise known as the Common Rule, is a system and a rule that works well but I say that recognizing with increasing responsibilities expected of the IRB as well as increasing complexity of the science by which IRB's need to consider when they look at ethical issues. There is no doubt that there is a need for improvement and to that end we look forward to NBAC's deliberations and advice in this particular area.

I am delighted to be here today having been invited. For many of you, I think for many people, for many researchers, when they think of NIH, they often think of the Office of Protection from Research Risks.

It is not well appreciated that although OPRR is administratively housed in NIH, it is responsible for implementing the human subjects regulations for the entire DHHS and, in fact, for many other agencies as well.

So I would like to spend my few minutes this morning telling you a little bit about what NIH does independent of OPRR in the protection of human subjects. You also are going to hear later today a report from Nancy Dubler and Renee Landers, who chaired a review committee that Dr. Varmus convened to look at the organizational locus of OPRR and to advise whether there is a need for OPRR to have additional delegated authorities.

I will not steal from their thunder but, as you may well know having been announced at the Advisory Committee to the Director, one of the recommendations is that OPRR should be administratively located from its present location within the NIH to the Office of the Secretary. The NIH has sent this report to the Secretary and we are awaiting her response.

So to that end I would like to, as I said before, address just a few things that NIH is up to. Maybe some things that people have not heard of.

There is a central resource at NIH called the

NIH Office of Human Subjects Research. This is to assist investigators. We, needless to say, have a large intramural program for which we conduct research, not only oversee extramural research but by which we conduct research. And OHSR has developed a computer based training module to orient NIH research staff to special requirements associated with research. Completion of this training is required by all NIH staff conducting human subjects.

In addition, you may well be aware that a former NBAC commission member, Zeke Emanuel, was recently hired by the NIH to enhance its department of clinical bioethics and Zeke is building up quite a program there that is engaged in many subjects related to NIH and related to NIH supported research and, in fact, I think going beyond that to many issues related to the bioethics of human subjects in medical venues, not just in medical research.

For our purposes, Zeke's department, Dr. Emanuel's department, provides bioethics consultation and sponsors educational activities and offers training fellowships but these are just two of many other activities that happen in the institutes and centers.

I know that you had spoken with Dr. Jerry Kirsch, who is the new director of the Fogarty Center,

and Fogarty has a new initiative on bioethical considerations in cross cultural research. They had a small meeting last week that began to explore these things.

You all may also be well aware of the longstanding and I think extremely effective ELSI program in the Human Genome Research Institute, which has been looking at genetics and bioethics issues for some time, discrimination in insurance and employment, informed consent in genetics research, public and professional education about genetics research and bioethics.

There are also some NIH-wide activities. A multi-agency initiative on training in bioethics and another to support the development of a short-term course in bioethics. Again the effort to try to create models that could be promulgated around the country to other sites.

Despite these many initiatives, NIH certainly recognizes that we must be perpetually vigilant about protecting human subjects, and we must continuously seek new ways to improve that protection in the current systems.

For example, NIH has already begun to think about if the Secretary makes a decision to move OPRR to the Office of Secretary, what are the remaining

responsibilities and what are the enhanced responsibilities that NIH may need to take up in light of that departure.

To that end, Dr. Varmus has asked the Trans-NIH Bioethics Committee to address this issue and which we will do so very quickly and put a report on Dr. Varmus' desk shortly. For those of you who have not heard about TNBC, it was put together about two years ago and was convened by Dr. Varmus about two years ago to identify and discuss bioethical issues facing biomedical research, in general, and the NIH in particular.

We have been spending a lot of time, in fact, addressing many of the reports that NBAC has been putting out and examining them from the NIH perspective, and I think you have heard from us on both stored tissue and on the decisionally impaired. We are now fully engaged in the issue of developing a set of principles for research in the protection, privacy and confidentiality of individually identifiable research information.

I end by just saying the issues that NBAC is addressing are extraordinarily important to NIH and we look forward to hearing from you and working with you as you proceed in strengthening a vital system to the continuation of research.

Thank you.

PROF. CHARO: Thank you, Dr. Skirboll.

Dr. Elizabeth McCormick from NASA.

BETH McCORMICK

NASA

DR. McCORMICK: Actually it is just Beth but I can accept an Elizabeth. That is fine.

I am appreciating the opportunity to represent NASA at this meeting of the Bioethics Advisory Commission. I am representing Dr. Arnold Nikkogosian (?) today. Dr. Nikkogosian has many responsibilities at NASA. He is the Associate Administrator for Life and Microgravity Sciences and Applications. He is NASA's chief medical officer and he is the designated agency safety and health official.

At NASA, the Office of Life and Microgravity Sciences and Applications is responsible for the health and welfare of the NASA work force. That work force includes a unique category of workers, the NASA astronauts, whose work environment certainly is not the typical desk job that many government bureaucrats experience here in Washington.

Given NASA's mission, our primary focus must be to protect the health and welfare of the astronauts who will live and work in space. There is a special commission to protect them from as many of the hazards as

reasonable from the harsh environment of space. This presents a special problem as well since NASA recognizes the right of the astronaut to be a free-willed research subject at all times with the right of the astronaut -- with the right of refusal to participate in research as human subjects at any time.

This means prior to selection for flight, after being selected for flight, and during the flight the check and balance to protect astronauts as commanded subjects is an ongoing process and, frankly, hard work.

It also must be recognized that during space flight the astronaut works not only as a research subject but as the laboratory technician and in many instances a surrogate on orbit investigator representing the ground based investigator in making necessary decisions, equipment repairs and clinical judgments.

Accordingly, NASA ensures the accomplishment of the proper written informed consent by the astronauts participating in shuttle missions. In terms of regular missions astronauts have full rights to accept or decline participation as human subjects with no loss of mission status. In terms of special life sciences dedicated missions, astronauts are selected for flight based on their agreement to participate as research subjects.

If an astronauts withdraws from any or all of

the experiments, NASA has promulgated rules stating that an astronaut may be dropped from the mission and another astronaut who volunteers substituted for that place. In principle, the astronaut will not be penalized for participation in future regular missions but may not be considered for additional special life sciences dedicated missions.

However, if the risk or experiment is changed once the astronaut has agreed to participate in the dedicated life sciences mission, NASA has agreed not to remove the astronaut just because the astronaut withdraws from experiments.

A new arena for NASA is setting policy with our international partners for the protection of human subjects that fulfill United States requirements while recognizing the differences among cultures. An international institutional review board has been established for approving research on human subjects that will be performed on the international space station. This includes the European Space Agency, Russia, Japan, Canada and NASA.

The international IRB approves not only the actual experiment procedures for space but also the training necessary for participating in the research. Each host space agency must approve an experiment by

their in-country IRB before it is presented to the international IRB.

Additionally, if the experiment will be performed on the NASA shuttle, the NASA IRB at the Johnson Space Center, which reviews all U.S. space flight research using humans, must prereview and approve the research. This process is just being started and we certainly are carefully monitoring the potential and real problems that could occur.

We are considering issues such as whether the NASA IRB will approve the experiment on an American astronaut which will be done in another country and not on U.S. soil.

Another area of concern has been the aspect of multiple experiments on individual subjects and/or making certain that principal investigators are providing appropriate safety and informational knowledge to the research subject.

NASA has instituted as a trial a requirement at the Johnson Space Center that a medical compliance officer be appointed and observe on site research on human subjects.

A flight surgeon or other representative of the IRB is also assigned for each mission and observes all research in which the assigned astronauts

participate.

Finally, NASA has had a policy in place requiring members of research populations to participate as IRB committee members. This has been most successful at the Johnson Space Center where current astronauts over the last 15 years have served as voting members of the IRB. Their input has been invaluable in highlighting to other IRB members the frustrations and rewards of serving as astronaut research subjects.

In conclusion, we at NASA are working diligently to protect human subjects. We have enlisted the aid not only of experts within NASA but also work with ethicists in the academic community such as Dr. Barouche Brodie, and have worked with closely with Dr. Ellis at the Office of Protection from Research Risks.

Again, thank you for this opportunity to address the NBAC.

PROF. CHARO: Thank you for coming.

Dr. Barbara Levin from the National Institute on Standards and Technology.

DR. BARBARA LEVIN

NATIONAL INSTITUTE ON STANDARDS AND TECHNOLOGY

DR. LEVIN: Good morning. Today I plan to bring you up-to-date with regard to our efforts in human subject research.

My primary position at the National Institute on Standards and Technology is a scientist but I am also the chairman of the IRB. The National Institute on Standards and Technology was formally known as the National Bureau of Standards or NBS and most people recognize it as that under that name. We are a part of the Department of Commerce.

I became chairman of the IRB in October of '96 and met with the NBAC staff in May of '97.

NBS or NIST has been reviewing human subject research since the early '70s and the committee who did these reviews was called the Human Research Ethics Committee until this year when we finally changed it to call it the Institutional Review Committee.

We do not do a lot of human subjects research at NIST, maybe a dozen projects a year and most of these are low risk, but we do try to do a conscientious job.

Since meeting with the NBAC staff in '97, we have implemented additional mechanisms to deal with the various situations that arise.

In November of '98, we revised the chapter in the NIST administrative manual to reflect these changes. I brought a copy of that new chapter here.

One change was the delineation of how and who determines whether a research project is exempt.

Previously we had not used this option.

We have also included another level of review. All proposals approved by the IRB are sent to the Deputy Chief Counsel of NIST for his concurrence. He also has to concur with all exemptions. All approved proposals that have the concurrence of the legal office then go to the Director or the Deputy Director of NIST for final approval.

Other mechanisms that were updated are those situations other than research at NIST by NIST scientists. For example, collaborative research being conducted both at NIST and at outside institutions and research funded by NIST but done elsewhere.

Finally, we are in the process of putting a web page together, which will help the scientist at NIST to understand what is needed in putting a proposal together for the IRB.

Our approach has been to help the scientists to get their research approved and conducted in compliance with the federal regulations.

Thank you.

PROF. CHARO: Thank you and thank you for coming.

Dr. Stuart Plattner from the National Science Foundation.

DR. STUART PLATTNER

NATIONAL SCIENCE FOUNDATION

(This speaker's testimony contains inaudible portions due to technical difficulties with microphones.)

DR. PLATTNER: While these comments are based on my experience as an NSF human subjects research officer and reflect the opinions of my colleagues at NSF, they are not an official statement of NSF policy.

It is often said that where you stand on an issue is where you sit professionally. Where I sit at the National Science Foundation human subjects are involved in a tiny portion of the extramural research that we fund mainly in social and behavioral sciences and the majority of these deal with human subjects in ways that represent research. Most of NSF human subjects research awards are exempt or qualified for expedited review under the Common Rule.

So my message is simple, the rules and procedures the government develops to protect human subjects from potential harm due to involvement in research activities, one size fits all straightjacket that subordinates no or minimal risk projects in the same bureaucratic rate of oversight that high risk, namely biomedical research, deserves and demands.

An anecdote will make the grounds for this

position clear. Last week -- no, it was a couple of weeks ago -- I got a call from a young PI at Duke University from the Arts and Science, not the medical school but it is IRB research. The researcher was a (inaudible) scientist linguist whose research involved asking children in Japan the meaning of words and she was an Hispanic. Her sponsoring project's office was going to revoke her permission because the original IRB review some years ago insisted that she constitute an additional (inaudible) in Japan (inaudible) research.

When I looked at her research file I realized that the project was not under the rules involving interview procedures when no information was elicited that can reasonably be expected to harm the respondents. When I spoke with the Duke sponsoring project's officer she was relieved to hear that no additional oversight was necessary and admitted that they were all (inaudible) medical IRB (inaudible).

Perhaps the time has come to seriously consider a two track system separating the generally higher biomedical research IRB review from the generally lower risk sociobehavioral research IRB review.

At least we should always be aware that the burden of bureaucratic oversight should be proportional to the risk subjects can reasonably be expected to incur.

Thank you.

PROF. CHARO: Thank you, Dr. Plattner.

Dr. Jim Shelton from the Office of Population at USAID.

DR. JAMES D. SHELTON

U.S. AGENCY FOR INTERNATIONAL DEVELOPMENT

DR. SHELTON: Good morning. I did submit six points in writing and I am going to make the sanguine assumption that everybody has had a chance to read those and I am going to respond to some extent what people have said.

Reflecting upon what USAID does, I think it is important to recognize that we do a lot of different kinds of research but research is only a tiny part of what we actually do and a lot of the research that we do is programmatic, public health and social science so I have to say that I do sympathize and, in fact, support the comments -- a lot of the comments that Dr. Speers and Dr. Plattner has made.

I think on the one hand we have a system that is working reasonably well but I think also it is a system that is creaking and it is creaking because of burden. If I could sort of capture my major concern, I guess I would say that the balance between process and substance is out of whack.

On the one hand, I see situations like Dr. Plattner described where there is a lot of process, which does not seem to have a lot of reward for it.

On the other hand, I worry that there may be significant things that because the system is more of a trust system and is so over burdened by the paperwork that people do not have the chance to really focus on the more important things.

So, I think, you know, what we really need to have a system that has better protection on the one hand but less burden. I think it is important to recognize that the common rule has worked but it is really a very difficult instrument, I think, for me to work with and I have worked with it for a number of years. I think for people that are not that experienced with it, it is very daunting. I think that is a lot of the problem that we face.

You know, we really want a system to get better ethical behavior where the participants will embrace it and, unfortunately, I think we have a tool that is not very conducive to that. And I think there are things that we can do sort of big and small to try to remedy that but I would point out two of them that I think have occurred already. One is that we had sort of collective activity in the subcommittee to try to develop

a guide on how to interpret the common rule and I think you have a copy of that.

I think another excellent example is the exercise that was led by OPRR and FDA on expedited review that occurred, I guess it was last year, that I think really improved, I think, the -- tried to get at what I was trying to make sort of to shift the burden to more impact and less process but I think there are a lot of other things that we can do.

Thank you.

PROF. CHARO: Thank you, Dr. Shelton. Ms. Blanca Rosa Rodriquez from the U.S. Department of Education.

BLANCA ROSA RODRIGUEZ

U.S. DEPARTMENT OF EDUCATION

DR. RODRIGUEZ: Thank you very much.

Good morning, members of the commission and my fellow colleagues from other federal agencies.

The mission of the Department of Education, shortly, is to provide simple access to educational opportunities for all students. Presently in the Department of Education, we have a very formidable large discretionary grant program and formula grant program that totals up to about $22 billion in FY98 and expect certainly that it will increase for FY99. That

represents about 10,600 awards. These awards are both formula and discretionary grants. About $2.8 billion is discretionary grants.

Our preliminary inventory last year of research activities in the Department of Education that was completed by various program staff in all of the program offices in the department yielded initially about 500 research projects that conceivably would fall under the policy for the protection of human subjects.

I, as the director of grants policy and oversight, the function in the department where the Part 97 is being implemented across the department, have worked very closely now with staff in my office and then staff throughout the program offices to begin integrating our policy related to the protection of human subjects throughout all of the policy guidance for grants policy for program managers throughout the various offices.

As you know, we in the department have sort of been on a fast pace to implement the policy and, in fact, in a very short time with quick turn around since 1988 have begun putting in place an infrastructure to support program offices and the implementation of this policy with grantees.

In fact, at the last commission meeting, we were just about getting started the last time I reported,

in fact, any activity in the department, and that was around September of '98. So since September of '98, in fact, you know the department has set aside about 1.5 FTE in the office to begin with implementation of this policy and then very quickly we moved on to adopt subpart D of additional protections for children and that moved very smoothly through the department and then as quickly we were able to get on board adopting an intramural research directive that was signed by the Secretary.

Shortly after the intramural research directive was signed then we set up an institutional review board and we now have an institutional review board for the department and a chairperson. And Ira Pritchard in the Department of Education, Office of Educational Research, is the chair of that board.

The board has met. The board has received training and the board is -- and the members of the board are intimately involved with my office in helping provide and support that infrastructure as we move along in the implementation.

In addition to the intramural directive that has been signed by the Secretary, we quickly then moved to pull together the extramural research directive, which was additionally drafted, and we now have -- the last time I talked to you we were in the process of drafting

it. We have now signed that and have moved to implementation and training program offices.

Not only the training but we have a number of awards, new awards for FY99, that are now being reviewed under that policy and this would be awards that are primarily in the Office of Special Education and rehabilitative services, awards that have been made in the Office of Educational Research Improvement and the Office of Post-Secondary Education and International Education.

These awards -- what is happening essentially is before the award is obligated, my office will review the proposal and determine to see if it is exempt or if it is -- requires assurances and IRB review. Before the award is obligated the grantee is contacted and the program office is contacted to make sure that all of the documents are in place and the assurances have been received by my office before approval is given for the obligation.

I will say to you that this is the first time that the department has engaged in this activity with our program staff. We have, I think, made a superb effort to negotiate assurances where they are required and I must say that I think some of them still fall through the cracks as program staff and grantees attempt to learn the

new way of doing business with this new policy and new regulations.

As we have -- as we are learning from the experience ourselves, we are extending the benefit of that experience to also begin identifying the noncompeting continuations and those would be the FY98 awards that conceivably will also require IRB review and have now engaged in a communication with the grantees as well as the program offices to obtain the required documentation and assurances if, in fact, the project is not exempt.

There is also the consideration that there is a culture in the department which already has a voluminous amount of activity going on and responsibility related to monitoring the existing grants and so that in many cases the addition of Part 97 is another layer of work and requirements that is -- you know, sometimes not whole appreciated and so thereby sets back the award and the obligation because the department does have a goal and we are in a pace to make awards by May 31st and that -- because want to give grantees the opportunity to hire staff, quality staff, and get the program in place, set the program in place.

So we have a lot of competing activities with the Part 97 but nonetheless we do have a commitment in

the department to make sure that the process is -- indeed, there is integrity to the process and, indeed, the assurances are negotiated.

I would like, before I close, though say that I do support Dr. Pat Plattner's position. You know, the kind of research we do in the department is primarily social science and the inquiries and the research that we support for most cases are exempt from the common rule but, as I said, we are engaged with program offices to learn more about the research and provide the training so that we can proceed with this with full integrity and compliance.

Thank you very much.

PROF. CHARO: Thank you.

Dr. Tim Gerrity from the Veteran's Affairs.

DR. TIM GERRITY

DEPARTMENT OF VETERAN'S AFFAIRS

DR. GERRITY: Thank you, Mr. Chairman and commission members for the opportunity to speak to you today about the Federal Common Rule for the Protection of Human Subjects.

My name is Dr. Timothy Gerrity and I am the Special Assistant Chief Research and Development Officer for the Department of Veteran's Affairs. I represent VA on the Human Subject Research Subcommittee and the

Committee on Science of the National Science and Technology Council.

Since 1998 I have been responsible for the continued implementation of the Federal Common Rule in VA. My statement today reflects the opinions of myself and my colleagues within the Office of Research and Development in VA and does not necessarily reflect policy of the Department of Veteran's Affairs.

In 1991, the Department of Veteran's Affairs became signatory to the Common Rule, which was incorporated in the VA regulations as 38CFR16. In 1992, VA also adopted the Common Rule as Chapter 9 of its Research Policy Manual, M3 Part 1.

To provide you with some perspective on the implementation of the Common Law in VA, let me briefly describe research in VA. VA research is an exclusively intramural program with approximately 4,000 active investigators in over 150 VA medical facilities across the United States.

In fiscal year '99, Congress appropriated $316 million in funds that go directly to fund research. In addition to appropriated research funds, VA researchers in local VA medical centers also bring in funds from such sources as NIH, CDC, private foundations and pharmaceutical manufacturers. Typically these funds

exceed the appropriated dollars VA receives in its research budget. When that is overlaid on top of the overhead that we are provided from the medical care appropriation to VA the total amount of research funds available to VA researchers is approximately $1 billion.

The overall research program is managed centrally at VA headquarters in Washington through the Research and Development Office or RDO. Research policy, including policy on the conduct of human research and centralized peer review mechanisms are managed from headquarters. Headquarters distributes research funds to the field on a peer reviewed merit system.

The RDO manages four research programs, medical research, health services research and development, rehabilitation research and development, and cooperative studies. A program of multisite clinical trials.

Most major VA medical centers have formal affiliations with nearby universities and many VA investigators are also faculty members of the affiliated universities. Approximately three-fourth of VA researchers are clinicians, with the remainder being Ph.D. Because one of VA's mission is to care for sick and disabled veterans, VA is proud that a significant amount of is research is clinical and much of that

involves research on human subjects.

Over the years, VA research has contributed significantly to the understanding and treatment of cardiovascular disease, mental illness, AIDS, addiction and diseases commonly associated with aging such as Alzheimer's and Parkinson's.

Each VA medical center has a research program office that provides local research management and leadership. The office is directed by an associate chief of staff for research who is usually a clinician researcher him or herself. The local research officer has many functions. Among these, is the management of local institutional review boards. In VA these IRB's are called Human Subject Research Subcommittees of the Local Research Development Committee. Because the term IRB is more familiar I will use that term to denote VA Medical Centers Human Subjects Research Subcommittee.

Depending on the breadth of funding sources for human research conducted at local medical centers, a variety of methods to provide assurances to funding agencies are employed. Some VA medical centers are joint signatories with affiliated universities under a single or multiple project assurance with the NIH Office for Protection from Research Risk.

Other VA medical centers have their own MPA's

with OPRR and other medical centers, usually those with small human research programs, rely on single project assurances and other means of providing assurance to appropriate funding agencies.

In addition to medical center IRB's, the VA operates more national IRB's that are responsible for initial ethical review of VA sponsored multisite cooperative research projects. Each performance site of a cooperative study must also provide its own ethical review by the local IRB.

I would like to address now several issues related to the Common Rule and the impact of its implementation on the Department of Veteran's Affairs human research programs.

The Federal Common Rule is a great leap forward in establishing a uniform set of policies that all federal research funding agencies and departments could adopt and implement. However, from my personal perspective within the VA Research and Development Office, the ease and uniformity of implementation has been highly variable. The reasons for this are not readily apparent but I will offer some observations of my own.

The language in the Common Rule is complex and proscriptive and written in a legalese that is often

impenetrable particularly to field researchers and members of IRB's. Interpretation of the language is often left to individual funding agencies, though they are free to seek the generous assistance of the Office of Protection from Research Risk. VA has frequently availed itself of this assistance.

The language of the Common Rule is geared toward a biomedical research paradigm with inadequate attention toward other human research paradigms such as in the social sciences.

Responsibility for interpretation and enforcement of the Common Rule was never quite clear, only to the power accorded by the Common Rule to OPRR. Specifically, a multiproject assurance granted by OPRR to an institution provides assurances to DHHS but also must be accepted by all other funding agencies in providing assurance to them. This has placed OPRR in an extraordinary position where it can virtually interpret federal regulations for all other departments and agencies.

However, if an institution receives little DHHS funding, OPRR may choose on its own to not grant an MPA to a particular institution, instead relying on single project assurances. The institution then does not benefit from the lack of coverage by an OPRR MPA and must

negotiate separate assurances with each individual funding agency. This can create great confusion and large paperwork burdens to the local VA medical center. An example of this problem was illustrated by the recent events at the VA Greater Los Angeles Health Care System.

OPRR deactivated the GLAHS multiple project assurance in March of this year. Although there was justification for OPRR to act against GLAHS, the deactivation of the MPA was prompted both by concern over problems with GLAHS's IRB as well as the presumption that GLAHS did not need an MPA because so few projects there were HHS funded.

It was only after OPRR deactivated the GLAHS assurance that it became aware of the breadth of non-HHS funded research granted directly to GLAHS as well as HHS funded funds granted to GLAHS as an affiliate of UCLA for human research that was conducted both at UCLA and GLAHS. The actions of OPRR affected hundreds of human studies.

Depending on the particular circumstances, OPRR alternately claims jurisdiction only over HHS funded research or over all federally funded human research. These different positions frequently cause confusion in local the medical centers.

I applaud the decision by HHS to move OPRR into the Office of the Assistant Secretary for Health at

HHS. I would, however, encourage Congress and the Executive Branch of the Government to give thought to the establishment of a single assuring authority that would provide uniformity of interpretation and enforcement of the Common Rule across all agencies. There is adequate precedent for this.

The Nuclear Regulatory Commission licenses all research facilities using radioactive byproduct material for biomedical and other research. This licensing procedure is independent of the source of funds for the research conducted using byproduct material.

By no means should my comments be interpreted as a criticism of the dedicated and hardworking people who staff OPRR. They, themselves, do an outstanding job of coping with the extraordinary responsibility with a woefully inadequate staff.

Another problem with the Common Rule is its failure to encompass research not funded by the Federal Government. For human research conducted at VA facilities this is not a problem because all research regardless of funding source conducted at a VA medical center is considered VA research and thus, by default, is federally funded.

However, thousands of privately funded human research studies are conducted in the private sector

without the assurance of the twin protections of scientific peer review and the effective informed consent that all participants in human research are entitled to.

This is a concern for the Department of Veterans Affairs because we have a constituency, namely veterans, which may be victims of unchecked research. The health problems of Gulf War veterans are a case in point. Many sick Gulf War veterans are desperate for answers and treatments that sound medical science is not able to satisfy in the desired time frame. These veterans are often prone to offers of diagnostic tests that have no demonstrated sensitivity and specificity, and treatments with no proven efficacy or effectiveness. Many are invited to participate in poorly designed trials that have not undergone any peer review or ethical review.

For example, veterans have been solicited over the internet to provide a particular researcher with samples of their blood both for the purpose of research and an implied promise the tests will reveal the nature of their illnesses. The basics of informed consent were no where present.

Mr. Chairman, the Department of Veteran's Affairs is dedicated to the ethical conduct of human research. I am proud to say that in the past year VA

became the first federal agency to provide human research subjects the assurance that should they be harmed as a result of participating in VA research, VA will provide all necessary medical care to mitigate such harm. Many of the men and women who have served this country in times of peace and war also participate in VA research and thus continue to serve their country. As we owe veterans the best health care, we also owe them the dignity, benefits and justice of ethically sound research.

PROF. CHARO: Thank you very much, Dr. Gerrity.

Are there any other representatives of federal agencies who are now here who have not had the chance to present?

Let me then just say as we move into the discussion that we would welcome written statements from any agencies that have not yet submitted them. They are not required obviously but we welcome the materials. They are extremely useful because NBAC's interest is in understanding how to make the human subjects protection system both more effective and more efficient simultaneously.

In discussion with Dr. Shapiro yesterday, it emerged that he shares, I think, a widely shared interest

here so as the discussion proceeds it would be very helpful if people could keep in mind the possibility of explaining perhaps in somewhat more detail first how the exemption and expedited review process has worked for them as a means to separate the regulatory burdens for low risk or no risk protocols from those for protocols that, in fact, present significant risks to subjects.

Frequently, we hear, as we did today, that there is concern about the degree of process associated with low risk experimentation and a call for a second track of review, expedited review and exemption is designed to provide a version of that second track. It would helpful to understand better why that is not functioning adequately for those who have been talking about this.

The second theme that emerged from the conversation with Dr. Shapiro had to do with the prospect of a central office in the Federal Government that is responsible for some number of protocols that present special issues or that would function to become a source of common guidance and reactions to the situations in which that might be useful to your agencies as well as speculation about ways in which that might actually be an obstacle would also be tremendously helpful.

So if you can keep those in mind as you are

responding to the questions and discussion that emerges from other commission members that would be very valuable information for us.

Larry Miike?

DR. MIIKE: A question for -- any of you can answer, DOE, CDC or NSF, on the issue about survey or community intervention research or generally population based research, I know all of you have expressed some dissatisfaction with the current rule. Can you comment a little further, particularly on the informed consent and the risk level aspects of that?

DR. PLATTNER: Well, at NSF, just speaking for NSF, we do not do research ourselves. We give grants mainly to universities and we put the burden of responsibility on the university IRB to uphold the regulations so I have no direct experience with what you say unless I am misunderstanding your question.

DR. MIIKE: Well, what I am saying is that you could either go down a separate track or you can use the exemption and expedited review but the issue to me is around whether these should be exempted, expedited or separate, treated separately is the issue about the level of risk and the informed consent issues so how would you address those things in the kinds of research where you say that the -- and I think we all agree that in these

kinds of areas there really should be some different way of looking at it. I am just more interested in the specific issues about how do you deal with the risk level and how do you deal with the informed consent issues.

DR. PLATTNER: Well, in that sense at NSF we put the responsibility on the cognizant program officer, the NSF employee who is administering that grant, and that person by our regulations has the responsibility to safeguard the rights of human subjects whether or not an IRB declares something exempt. The NSF program officer can override that IRB and refuse to make a grant without either --

DR. MIIKE: I understand but we are talking process. I am interested in content. For example, minimal risk is defined as the risk of every day living and we know that that has been unsatisfactory when we are looking at human biological materials reports. I am more interested in whether any of you have some advice for us on the issue about what is inadequate consent and when does -- is consent always necessary and, if so, what is minimal consent, what is adequate consent, what is the risk to someone --

DR. PLATTNER: Well, if I understand a little bit of your question, to me the -- what I would do is to back up and say were there no biomedical research, how

would we go about dealing with social science research and -- I mean that sort of totally frames it in a different way. Instead of trying to say how can we make a wrench into a hammer or whatever and use it as a hammer, how can we design a hammer. And I think that to me one of the biggest problems is that informed consent is an almost all or none thing. Either it is the eight points or else it is waived or else you can -- you can modify it but it is kind of difficult to do that.

To me some kind of concept of permission that would be -- just for as an example -- that would be applicable to whether something is exempt or not. I mean, even if social science research is exempt under the current rules, you know, ordinarily you still want to ask permission unless there is some -- you know, you want to do a mystery study or something like that. So, I mean, that is one response.

DR. SPEERS: Let me see if I can give you some information on that and think of it -- sort of think of it in two ways. One is this -- one is the issue of the level of review and the level of review being commensurate with the amount of risk. For survey research there is the possibility to exempt it from review and what an exemption means is it is exempt from the policy, exempt from the federal regulations. That

actually means two things. One is that the research institution if it does not have a multiple project assurance, does not need an assurance.

And, two, that the project does not need IRB review nor does it need to meet the requirements in the regulations. One could take that point sort of to its absurdity and, therefore, say that one does not have to get informed consent because it does not have to meet the requirements in the regulations.

That is troublesome because even though a survey may be of little or no risk, there is still -- I think we would all agree -- an ethical way to conduct the survey. One should still tell individuals something about the purpose of the survey, you know, what it is going to entail and ask for permission. It is hard for me to envision how you can call someone up on the telephone and start to ask them questions. You know, there still needs to be some kind of informed consent process.

The issue, though, in part is that if you do decide to review it under the regulation then it gets reviewed essentially the way research that is of more risk gets reviewed. It is hard to differentiate in the regulations what should be applied and what should not be applied. Even though under informed consent it is

possible to waive consent or alter the consent process there is not good guidance as to how necessarily to do that. Of the eight essential elements of consent, which ones should definitely be in there for every survey, which ones should not be.

When you look specifically at the criteria for waiving documentation of consent, those who -- criteria, which you use one, you can waive under either one of those two, the one that is particularly troublesome for survey research is the one that states that the survey is minimal risk and involves no procedures for which one would normally get consent. That sounds very much like a criterion that might be used in a medical or clinical environment. It is hard to find the analogy in every day life that fits for something like survey research.

So I think that the issues around consent -- if I could just summarize -- there are two. One is this issue of documentation of consent and survey research and whether oral consent essentially is sufficient. And then the other is how one -- what one needs to say, what is adequate informing in that situation.

PROF. CHARO: Other comments from the agencies on this point? Dr. Levin?

DR. LEVIN: I have a comment. Since we

recently started using this option of declaring certain research projects exempt, I am not sure that this -- and this, of course, is for very low risk type research. I am not sure that we are really saving a whole lot of time for it to be declared exempt. Somebody now needs to make that decision. The researcher has to put together the entire proposal and fill in all the forms so that the person who would now be making this decision can do so with the information that that person needs.

What we have decided at NIST is that the -- NIST has a director and then it is divided into laboratories. Anybody wanting to do a research project even if they, themselves, think it would be exempt fills out all these forms. They usually confer with me to make sure that they have filled out these forms correctly. That takes some time back and forth.

It then goes to two levels of administration, their group leader and division chief, to declare whether this research is scientifically sound. They are deciding whether it should actually be done or not based on just its science. It then goes to the director of the laboratory who now reads it and decides if it is exempt or not.

If it is exempt it then comes back to me and I tell the researcher that this project is now exempt.

They do not have to worry about any further administration of this according to the Common Rule. That can take as long as a month of time to go through all those stages.

If they decide it is not exempt it comes back to me and then it goes to the IRB and the committee makes its decision.

Oh, I am sorry. There is one more point in the exemption. After the director of the laboratory decides that it is exempt, it goes to the legal office who has to concur so that is an additional step.

PROF. CHARO: If I may ask a question about this. Having worked ever so briefly in the Executive Branch I can fully believe what you described, the series of signature sign-offs you need.

Since you described your procedures as being fairly new --

DR. LEVIN: This particular aspect.

PROF. CHARO: Yes. Do you think it is likely that as the investigators at the National Institute on Standards and Technology become more familiar with the Common Rule and its exemption provisions that that procedure that has been designed might be streamlined somewhat so that there is a more abbreviated process by which investigators can self-identify the key criteria

that make them eligible for exemption and limit the number of sign offs to one or two and the process take several days rather than a month?

DR. LEVIN: I actually do not see that happening. Right now -- I mean, we put this new subchapter of our administrative manual together and it tells you all the steps one needs to do. I think a lot of scientists would like to say, and they have, they come to me and they say this is exempt and I am not -- you know, I should not have to do anything but somebody has to make that decision and I think the reason that we had not used that option before is I feel that is a lot of responsibility to say, well, this project is exempt and this project is not exempt and it was pretty much on the shoulders of the chairman of the IRB.

Now it has been taken away from the chairman of the IRB and is put into more the administrative category there with the concurrence, as I say, of the legal office and I have had one situation where the director said it was exempt and the legal office said, "No, it is not exempt."

So this does take time. I think we are doing a conscientious job but I do not see one way of how to streamline it.

Now, again, people say, you know, this should

not take this much time because it is such low risk. I mean, in some cases they are just getting blood from some place and they have no idea who is giving the blood so it is anonymous blood and they are going to be doing studies on this blood but it still goes through this whole process.

PROF. CHARO: Dr. Skirboll, and then we will go back to the order questions.

DR. SKIRBOLL: This relates but I think we have -- at least at this point the discussion has been focused on behavioral and social science research, and one of the things that I would like to bring to the commission's attention and would like to hear is this issue about what is risk, especially as it relates to, I think, new sensitivity of society to privacy and confidentiality.

There is much discussion around the table about risk associated with biomedical research, which is intervention, and risk is commonly understood. But risk with regard to knowing and risk with regard to others and yourself knowing, I think is a new concept and that the commission -- that all of us would benefit from some guidance about what is risk in that regard. I think that is particularly relevant to what we have considered previously as low risk, certain areas of social science

and behavioral research.

PROF. CHARO: Dr. Jonathan Moreno? For those of you who have not been introduced yet, Dr. Moreno has joined the NBAC staff as a contractor to work on the report concerning the human subjects protection system in the United States.

DR. MORENO: Thanks, Alta. I have listened to this discussion with great interest as I have a neighbor in Charlottesville who is a professor of psychology or I should say an assistant professor of psychology who is feeling the publication pressure and about every time he sees me, walking his dogs, he takes the opportunity to complain to me about the hoops that he has to jump through to get his survey research approved by the UVA Arts and Sciences IRB. It reminded me of the case of the young professor who is trying to get her work done in Japan.

I point out to him about every third time I see him that this is probably not because of the pointy-headed ethicists but has something to do with the fact that local protocols often require more hoops than are, in fact, required by this system. And it seems to me that some of this is going on both in institutions and perhaps in federal agencies. The risks that people are worried about often are publications risks and legal

risks or perceived to be such rather than perhaps the risks of the research itself.

It strikes me that this is to some extent a cultural problem, that is to say not only a cultural problem within our universities and our federal agencies but maybe also within the society at large, though I am not a sociologist. We are very concerned about not getting all the right sign-offs and we do not know that it is minimal risk until all the right people say it is minimal risk.

What do we do about that? How do we engender a less anxiety ridden system?

DR. PLATTNER: I think I know what we should do and I think OPRR should be much, much more aggressive and much, much more active in educating IRB's about the leeway that currently exists in the Common Rule. They have a lot of leeway but what happens is -- as I have told you in my little anecdote -- they get terrified. I mean, they do not -- they are not paid to have their university's name appear in the newspaper in kind of a scandalous article so it is easier for them to be terrified than to assert the authority that the regulations give them.

I think the responsibility lies on the federal government, in general, and on those

organizations in the federal government that are charged with overseeing the Common Rule and that is OPRR.

DR. MORENO: But surely some of that responsibility also lies with the local institutions to get clear on what the requirements are. Isn't that right? I mean, be accusatory. I come from a university. Are we doing enough, do you think, to let the people who are dependent on your funding know what the rules are?

DR. PLATTNER: I do not know.

DR. MORENO: Thank you.

DR. PLATTNER: I am a program officer. In my real life I deal with grants to universities and I cannot tell you how often I get calls for help from researchers and I refer them to their local sponsor projects office and the help they get there is absolutely abominable and the reason is that even the great universities like Harvard put people in jobs with absolutely no training, no preparation, and yet those people have the authority to grant or withhold the ability of a researcher to do his or her project. It is a terrible situation.

DR. MORENO: Thank you.

PROF. CHARO: Diane Scott-Jones?

DR. SCOTT-JONES: I would like to comment on an issue that is related to the discussion that is going on now and I am especially interested in these issues as

they relate to research with children, and there are special sections of the federal regulations that apply to children, and I would be interested in hearing how you see those regulations for children. I just had circulated to the commissioners the Ethical Standards for Research with Children that is from the Society for Research in Child Development.

I think part of the educational issues that Dr. Plattner is raising rests not just with IRB's but with graduate training programs where everyone who is becoming a researcher should be educated about the ethical conduct of research but there -- I am sympathetic to the need to reduce paperwork and to reduce burdens on researchers but those burdens exist for a reason, and it is to protect parents and to protect children.

And there are risks of social science research, and they may be, as Dr. Skirboll has said, the risk of knowing and the risk of others knowing. They are nonetheless legitimate risks and I think even the example that Dr. Plattner gave where the researcher was told that her work was exempt, as I read the federal regulations that researcher's work would not be exempt because it is covered under the regulations, the subpart related to children, not the general regulation on survey research.

So I think we need to give more concern to

the special case of research with children. The issues like parental consent, the assent of the child, and many other issues that come up in research with children and adolescents.

PROF. CHARO: If I can just add one thing to what Dr. Scott-Jones just said, because you focus so much on this example I would like to inquire further because although, as I understand, the National Science Foundation has not adopted subpart D and the special protections for children so that from the NSF grantors point of view the exemption would be permitted despite the use of children.

I also understood that the Duke University multiple project assurance pledges that university to subpart D in all its divisions, not only its biomedical. So that while NSF did not need to insist on special protections, Duke was, in fact, obligated to forego this exemption so that we have here both a question about the degree of protection that is needed, the process of making multiple project assurances across both biomedical and nonbiomedical research, and the dilemma of differing areas of expertise within the Federal Government where OPRR is highly aware of the details of the MPA because it negotiates them but the grantor agency may not.

I wonder if you might speak to both her point

about children's protections and also this issue about the kind of consistency of understanding of the rules that apply in a setting.

DR. PLATTNER: Well, the first paragraph of subpart D reads, "This subpart applies to all research involving children as subjects conducted or supported by the Department of Health and Human Services."

PROF. CHARO: Right.

DR. PLATTNER: So it is specific to research projects that are funded by NIH. This research project was funded by NSF, which has not adopted subpart D.

PROF. CHARO: I could be misinformed but I understood that Duke University had volunteered in its MPA to apply this subpart to non-NIH/non-HHS funded research. It would apply it across the university.

DR. PLATTNER: I have no knowledge of that. My knowledge is that the project itself when I read -- I got a call for help from a panicked researcher. She had been doing her research for five years. She was all of a sudden being shut down. She could not understand what the issue was. I went and got her file. It was not a grant from my program. When I read the file, according to our rules there was no risk to human subjects. It was a very, very simple situation so far as I was concerned.

PROF. CHARO: This, in fact, though, is

precisely one of the points about the division of authority within the Federal Government and the assessment of appropriate protections. We have got two concerns here. One is substantively what should the rules be for children in these kinds of settings as a general matter and secondarily once an institution has decided what those rules are going to be.

How do we make sure that everybody in the Federal Government is together on the fact that they understand what rules now apply in that setting because this may be a perfect example in which one office in the Federal Government at NSF is not fully apprised of the fact that this institution has made a deal with a different office in the Federal Government to apply standards that are not NSF standards?

So we have two questions here. The substantive one as well as the one about how to achieve some sanity at the level of federal regulation.

DR. SCOTT-JONES: Could I just add a comment to what Alta just said? The particular project in question is not one that is somehow unique to NSF. That same research could be funded at NICHD so, therefore, this, it seems to me, is an example of what you are objecting to, and that is unnecessary bureaucracy.

I mean, it is just, to me, unacceptable that

a project that could be supported in other places has different rules depending on which agency gives the money to do the research. That just seems to fly in the face of the spirit of this.

PROF. CHARO: Dr. Levin and then Dr. Shelton?

DR. LEVIN: I would just like to say that this is one of the issues that came up that caused us to rewrite our subchapter. Since we only signed off on the Common Rule, which is subpart A, and we have not signed off on B, C, D or whatever, children would come under one of the other subparts of this.

If, in fact, the researcher who wants to do research on children, the NIST IRB is now ineligible to review that particular proposal and it is regardless of how much risk. I mean, it can be as simple as just taking a sample of hair from the child. We are not able to now review that proposal. It has to go to an outside IRB that has OPRR multiple project assurance because they have signed off on all these other parts as well and have been approved.

So this particular -- it is in the subchapter. It has not actually happened yet. I am not sure where a NIST researcher would go to get an outside IRB that is OPRR approved in order to do this. So that has not come to the forefront yet but -- and it is

something I am not necessarily looking forward to but it is -- that is the way we will handle it.

Any of the vulnerable populations now will not be approved even if it is research being done by NIST researchers inside NIST. We feel we do not have the authority to approve it.

PROF. CHARO: Dr. Shelton?

DR. SHELTON: I guess, I was going to pick up on the spirit of what we are trying to do. I think that is good. Although I actually think one of the things we could do a better job on is trying to come to a better consensus of what sort of the values and principles really are. I am not satisfied that collectively we necessarily have.

PROF. CHARO: Can you speak a little more closer to the microphone? Sorry, Jim.

DR. SHELTON: Sure. On the issue of spirit related to risk other than harms, if you will, or other things of harms, I think it is important to try to think not just of research but if you are concerned about privacy, if we are concerned about privacy, I think we ought to be careful not to avoid sort of the double standard. In fact, it is kind of a counter intuitive double standard to me.

If there are issues of privacy that relate to

our health care system or to data collection or what have you, this is one of the problems I have with the definition of research, is that it is counter intuitive that if you become systematic about doing something then it becomes subject to regulation. If you are haphazard about it, it is not subject to regulation.

So I think -- and my own view is that the Common Rule is a fairly ineffective tool for dealing with these issues of privacy across the board and, you know, applying the sense of equity we ought to be, you know, thinking about that across the board and I do not think that your mandate has to be just research by the way. I think if you want to make recommendations you could make them more broadly.

Just one point on children if I may. One of the main problems I have is -- again probably because of where I sit -- we do so much that relates to adolescence in my field where we work, reproductive health, sexually transmitted disease, family planning and that sort of thing. I find it difficult to apply the regulations as they relate to children to adolescents and that is -- because they are not the same, and that is a difficult issue to struggle with.

PROF. CHARO: Did you want to follow up?

DR. SCOTT-JONES: Yes. I agree that

adolescents are different but the consensus right now is that they fall under this same expectation of parental consent if they are younger than 18 years of age or if they are -- or unless they are emancipated minors. So still there are many issues where parents should give consent for adolescents' participation where there is a great deal of concern because the adolescent is not able to understand the purposes of the research as well as a parent.

DR. SHELTON: I think the regulation is difficult to get us to the spirit of what you are trying to -- I agree with what you are trying to say. I think the regulation is not very -- is difficult to fathom through to get to where you want to go.

PROF. CHARO: Yes?

DR. RODRIGUEZ: For an agency that is this year beginning the negotiation process for assurances sometimes we seem to maybe push this to an extreme and say, you know, it does apply and you do need to negotiate it. But I think that there is a lot to be said for the partnership that is established between the agency and the applicant and the program officer.

In our agency the applicant self-identifies and once that occurs then we quickly then begin collaboration with the program office and then

immediately also with the applicant in order to address the issue of risk and then the extent of exemption if an exemption is applicable.

I think that in the spirit of what we are trying to do that is an important step and I do not think that we should look over it.

The other point that I want to make is in the Department of Education perhaps we sort of operate on two tracks. At the Center for Education Statistics where much of the survey work is done, the policy that applies there and that is used most often is the privacy act and already there procedures are in place as required by statute at the center for encrypting data such that there is, indeed, a high level of privacy already for the subjects in the particular survey.

For our research in the discretionary portion where it is more social science and not as statistical or quantitative, and survey, then we are hoping that the process of partnership and self-identification will bring us to that spirit of protecting subjects that we need to provide students.

PROF. CHARO: Dr. Speers?

DR. SPEERS: I wanted to comment on the content of subpart D, not on the inconsistency among the agencies. Basically we find subpart D adequate in terms

of providing protection for involving children in research. We have a couple of issues, though, that relate to perhaps interpretation of -- again of the regulations.

Specifically the definition of a child. We tend to use the legal definition generally for -- you know, for age 18, which works for 48 out of the 50 states in the country. But that is not what the regulations say in part. They are a bit more vague so sometimes we are not clear particularly in research involving adolescents and public health research that we might do whether, in fact, we are dealing with children or we would be dealing with adults given the definition.

Secondly, this part of the regs seems to rely very heavily on state law and not doing something that is inconsistent with state law.

However, few state laws specifically address the issue of research in children and there are laws -- the laws around emancipated minors, mature minors, while they state the types of rights that children may have, in no laws that we have researched have we found a state law that specifically deals with research. So again one is often -- an IRB is often having to make some judgment of whether they can generalize from a particular state law to the research setting.

That is a particular issue for us in public health where we again will not necessarily be doing what will be considered biomedical research.

We might be doing some type of epidemiologic research but we might be working in a sexually transmitted disease clinic where every state in the country has some type of law that relates to the treatment of children for STD's without parental permission. And so we are in the situation of trying to figure out whether if we are doing a study related to STD's, whether we need to seek parental permission or not given that the child may have come to the STD clinic without the permission or knowledge of the parent.

We also have questions, you know, regarding -- again we come back to survey research and public health survey research and how these regs relate to survey research, again looking at what the definition of a child is. Where it talks specifically -- if I am looking at this regulation correctly -- has not obtained legal age for consent to treatment or procedures involved in the research. Again, you know, what is the legal age for consent to participate in a survey if that is the procedure here in the research? It is just difficult sometimes to interpret these regulations from a legal or regulatory perspective.

PROF. CHARO: Larry?

DR. MIIKE: I want to ask a biomedical question. For the VA and the NIH, can you comment on any problems that you have or any issues that arise in multicenter research, including international research and longitudinal studies?

DR. SKIRBOLL: Well, that is a lot of areas of research. Let me say, you know, in general with regard to multicenter research, the -- this was really addressed earlier in the day. What is allowed by the regulation may not be acceptable to the institution and one of the issues that has been faced is the Common Rule allows a single IRB to review a multicenter trial, for example, but in many institutions, because of their own fear of litigation maybe, simply do not go along with that proposal.

NIH is, in fact, right now exploring a couple of model programs where we are really encouraging universities to use the single IRB concept but this is something that I think is not a reflection of regulation. It is a reflection of fear of litigation and maybe not unreasonable fear of litigation. So despite what we think should be do-able it is not always do-able.

One of the things that I think for biomedical research and it is true for social -- by the way, I

should say that NIH considers behavioral and social sciences research for our purposes falls under the rubric of biomedical. We do not consider biomedical only intervention research in which there is a therapeutic or, you know, some sort of physical intervention.

The balance for human subjects protection, you all know, I am speaking to the choir here, is the balance between allowing really important research that is a service to society to move forward at the same time that you protect our partners in research, the human subject.

The issues of bureaucracy or the balance for us that we hear from our investigators are the balance between too much regulation and perhaps not enough guidance. What needs to be done by regulation and what can be done by guidance? What can we do to help our researchers help to protect our patients? No one wants to conduct a study where the patients are not protected but we need more guidance and maybe not in the form of more regulation where somebody really has to follow a certain set of rules but where IRB's, patients and investigators get guidance.

Gene therapy is an arena in which the NIH guidelines have been enormously helpful and are constantly being revised to help investigators, without

regulation per se, to understand what are the things they should be looking at when they look at a study on gene therapy.

With regard to bureaucracy I would add one other thing that I think NIH is hearing and that is -- I do not know how you solve this because it is a resource issue -- where investigators feel that research is being held up or is not being moved quickly enough and, therefore, bureaucracy is getting in their way is often a question of resources.

Resources both at OPRR in terms of oversight, enough resources at their university devoted to human subjects protections, people who actually know the rules and can help investigators wind through the rules, and resources for the IRB so that the IRB can meet frequently enough, get through protocols, monitor those protocols and do that in a manner to which investigators can move freely forward with their research and at the same time protect patients.

None of us want to see what has happened in the papers of recent, which is, you know, random studies where I would venture to say no investigator in those studies went in there with the intent to harm a patient or to not fully inform a patient, or to have a patient not be adequately protected.

So in all of those arenas, longitudinal research, biomedical research, social science research, the balance is really, and I hope that you will all address that, the balance is really between what we really need to tell the community out there they need to provide resources to this arena, and do we need regulation in every area. Is there a way that we can provide guidance without setting up more laws?

And, finally, I think the thing that everyone is going to have to look at is the role of the state versus the regulation vis-a-vis the government.

So that is sort of the answer to the question.

PROF. CHARO: Dr. Susan Rose from the Department of Energy, I notice, has joined us since we began. Did you want to join the table and make a statement?

DR. ROSE: No.

PROF. CHARO: Okay. Feel free if you change your mind or you would like to comment on what you are hearing.

Other questions from commissioners or comments from --

DR. GERRITY: I just wanted to respond.

PROF. CHARO: Dr. Gerrity?

DR. GERRITY: You had also addressed your question about cooperative studies to VA. As I mentioned in my statement that cooperative studies within VA are managed with respect to ethical review by having first a national IRB review, which those IRBs are located at what are called our Cooperative Studies Coordinating Centers. And then each participating site must also -- we require it -- must also review the proposed protocol and the informed consent.

I would say we have been fortunate that -- and maybe in large part because it is an intramural program -- that we have achieved, I think, a high degree of cooperation amongst the various IRB's and the national IRB's so we are able to come to closure on protocols and consent forms so that we can move forward. So, as I said, it may be by just -- of us being an intramural program.

But I would also like to comment on what Dr. Skirboll said with regard to guidance as opposed to regulation. I think that the more that we can possibly move in that direction, I think the more we could reduce the fear sometimes that is inherent in the actions of institutional review boards as they act, particularly in the arena of high risk research protocols.

PROF. CHARO: Dr. Skirboll, and then Alex

Capron, and then Diane Scott-Jones.

DR. SKIRBOLL: Just one more short point in that regard. The issue of guidance, I think, addresses the issue that you raised earlier about a national -- so-called national IRB's. In large part, I think, NIH, and we hear from our investigators, believes in the importance of local review, how the IRB system is set up, that local review is important, that risk should be weighed at the site or at least within the context even of a multiple thing looking at it out there and not in a national context.

But in that regard the difficulty with local review has been absent of guidance, that people, as I said at the beginning, are being -- the IRB's are being asked to look at more and more complex issues, more and more complex science, and without more guidance -- in some cases very specific to where science is moving -- the tendency to move to national IRB's because of the need for expertise is what is driving it. So perhaps with more guidance we would be less inclined to move to the national IRB concept.

PROF. CHARO: Prof. Capron and then Dr. Scott-Jones?

PROF. CAPRON: Thank you, Alta.

The questions of federal oversight are

central to the mandate of this commission and it is refreshing to know that while we have been working on that subject, a number of the agencies reported today that prior conversations with and review with the NBAC staff and review of your activities have caused you to develop more effective internal implementation to adopt regulations or procedures for educational programs that you did not have.

And yet still it seems as though the examples that we have heard today indicate that one substantial source of problem is the continuing lack of uniformity, that the Common Rule is only a partial rule, and when different agencies would regard themselves as establishing different standards of review for the same project were it to arise in the Department of Education, the Department of Commerce, the National Institutes of Health, it would continue the very problem the President's Commission addressed in the early '80s and that led to this so-called Common Rule, which is the confusion that research institutions face when they have to apply different standards or given different advice by different agencies.

So one question I have is what stands in the way of the coordinating council or whatever the oversight group of which you all are members, I gather, moving

towards the adoption of all the subparts and eliminating the suggestion that parts B, C and D apply only to HHS sponsored work?

After I get an answer from any of you or collectively from you if you want to huddle about this, the question of -- I have another question specifically for the NIH if I could.

DR. LEVIN: I think one of the problems is to actually sign off on these other parts, and I may be wrong but we just went through this whole exercise of modifying the Common Rule to include classified research. This was done under the auspices of the Human Subjects Research Subcommittee and the 17 government agencies who had originally signed the Common Rule.

This was now given to each of the agencies, the parts that would now be the modification, and then we have to figure out how to get the Secretary of the agency to sign off on this.

This was not a minor effort, especially for somebody -- I am a bench scientist. I had to now figure out who do I go to. I mean, I did not feel like it was my place to go downtown to Secretary Daly's office and say, "Here, sign here." So we had to work this through the various levels of the bureaucracy.

I got the first signature, which I was very

proud of, done and then we found out in -- and I do not really understand all of the politics of this, that that was not sufficient because not enough government agencies had signed off on this and so then we had to come back and there is another form that now had to be also signed by the heads of all of these different agencies, and again I was successful in getting Secretary Daly's signature on that part of it.

I do not know at this time and place whether all of the signatures are in place. I would think for us now to get approval to be part of subpart B, D, E, we would have to go through that same kind of exercise.

Secretary Daly did sign -- it was not Secretary Daly, one of the prior secretaries of the Department of Commerce did sign off on the agreement that we would be compliant with the Common Rule.

PROF. CHARO: Dr. Shelton?

DR. SHELTON: I guess, I wanted to respond to the issue of uniformity and, I guess, simply to point out that kind of the flip side of uniformity is diversity.

A couple of things. First, we do have diverse mandates and we work in sort of diverse situations and so forth. And I guess one of the things folks ought to be cautioned against is, you know, some kind of monolithic approach to this set of issues which

is, you know, a very diverse and pluralistic, to some extent, set of issues.

And I guess, I think, that having some diversity in the process does promote some different ideas getting on the table that are useful.

PROF. CAPRON: Could I ask you to respond to this?

DR. SHELTON: Yes, I will. I was planning to.

PROF. CAPRON: The question because certainly the specific issue here -- if -- the example, and we are playing off of Dr. Plattner's example to a certain extent here. If research could be sponsored by NSF, by the Department of Education, by the National Institute for -- the National Institutes for Health, what -- what is the issue of diversity there?

I mean, if the same protocol -- and, I mean, one of the arguments that was raised was an IRB gets a protocol and the researcher says, "Well, I am planning to send this to the National Science Foundation." And they look at it and they say, "Well, if it is not funded by NSF, well, then I will send it to National Institute for Child Health and Human Development, or I will send it to the Department of Education."

Now the whole argument about the Common Rule

was that the IRB should be able to apply the same set of standards to the research. The people involved are not going to be different. The methods are not going to be different. The investigator is not any different. Why should they face different standards? All right. Well, we need a Common Rule.

Well, the Common Rule apparently does not extend across the full range of subjects. We have parts B, C and D to address special groups of subjects. But again those subjects are the same people whether the money flows from the United States Congress through one of these departments or another one of the departments. So I do not understand the diversity argument here.

DR. SHELTON: Well, I think I was applying it in a more macro sense. I mean, I think most observers would agree that this is a field that is changing over time and I think if it is going to change, the more sort of viewpoints and voices that are brought to bear on how it should change to respond issues of multiple sites and so forth. I was really responding to the more general issue rather than the issue on the various subparts.

On the issue of the subparts specifically, I mean, the fact is I think for most of us for the arenas that I think where we think it would make a difference, so much of what we do is regulated by OPRR at least as

far as I am concerned. You know, I think we feel that it is for all practical purposes largely taken care of.

PROF. CHARO: But if I understand the point correctly, the question is whether in an ideal world because we understand that these -- this system represents to a large extent the artifact to the way the U.S. Government is structured and the way in which regulations are adopted in different departments, and the prerequisites of different secretaries.

But in an ideal world would it be better to have a system in which special protections are geared to the special populations as opposed to special protections being geared to the nature of the funding from one agency or another so that, indeed, there would be consistency across the government depending on whether you are working with adults or children, high risk or low risk, invasive/noninvasive?

DR. SHELTON: I think -- I am just pointing out that consistency has a price. That consistency, you know, sounds like a good word and often times it is a useful concept but it also has a price to it and I agree. You know, the vagaries of our history -- there is lots of things in our society that are a function of who funds it, what state something happens in and so forth. Sure, that is an issue.

PROF. CHARO: Dr. Gerrity? And then we have got a few people over here.

DR. GERRITY: This discussion raises a point I attempted to make in my statement and that is if, for example, an institution has a multiple project assurance with OPRR then all other agencies that provide funds for human research to that institution are obligated to accept that assurance, which means, as I understand it, subpart B, C, D and E. However, if there is not a multiple project assurance with that institution then it is then subject to the different assurance processes for the different funding agencies and so there is some inconsistency there in that regard.

I would argue that one could not make a one size fits all policy but a policy that is flexible enough that it can accommodate the different needs of the different agencies and no particular concerns for their missions.

PROF. CHARO: I have --

PROF. CAPRON: Excuse me.

PROF. CHARO: Let me just take a moment just to kind of keep track of who wants to do things.

Okay.

Alex, I gather, you want to just follow up quickly on this.

PROF. CAPRON: No. I said I had two questions.

PROF. CHARO: Right. You reserved. Right. You had a second question.

Diane, Larry, Rhetaugh, Steve, Dr. Speers. Okay.

Second question, and then Diane.

PROF. CAPRON: The issue of regulatory burden is one which is, in fact, a reflection of some of the complaints that you have had here. It is interesting to hear people who are in a government agency say, in effect, that you get overwhelmed yourselves with these burdens and it is not just the researchers and institutions. But the NIH recently had a process, an initiative to reduce the regulatory burden, and I would like Dr. Skirboll, in particular, to comment. Although if others of you have taken account of what the NIH said in its document I would be interested to know the extent at which this has gotten broader attention.

Some of the proposals are ones which seem simply to require sort of a more common sense interpretation of rules. So the notion that annual review ought to be keyed to when a research project enrolls subjects rather than the date -- some arbitrary date on which it was approved if it takes six months to

get going and so forth. It is just common sense.

But there are other aspects of the changes that are much more substantive. While it is easy to understand why investigators would rather not make reports or would rather have greater flexibility and so forth.

I did not see any indication in this document that groups whose primary concern was subjects or who were made up of subjects or some cross section of subjects, or people who participate in research were taken into account, and I wonder what is the status of this NIH initiative, Dr. Skirboll.

Have any of these changes gone to the level where they are going to be acted upon? Is this a process that is anticipated to take years? Where are we with this regulatory burden?

DR. SKIRBOLL: Right. Well, the report is out. My understanding, the report was issued by the Office of Extramural Research and probably the right person to ask would be Dr. Baldwin, who is not here, but the report is out and I think NIH is in the process now of determining, you know, working with outside -- hearing from outside people about the report and then we will determine what we will implement and how we will go about implementing some of those changes within our

jurisdiction. Things that are not within our jurisdiction obviously we would have to work, you know, in the department or elsewhere to determine what it is we can change.

The idea of the report was really broadly to look at regulatory burden across the board and we will implement what we can, and hear from others. We are hearing a lot of feedback, a lot of positive feedback from universities about the value of the report and what is in the report.

PROF. CAPRON: Do you know if the department or the institute is taking any initiative itself to try to find out whether all the constituencies, including the unknown thousands of people who are human subjects and the disease based organizations or whatever that may represent their interests have reaction here or are you primarily listening to the people who are, in effect, burdened by regulations and are pleased to see anything you can do to lessen the requirements of the regulations?

DR. SKIRBOLL: No. We are hearing from everybody. Trust me. We are hearing, you know, from a lot of people who are saying that this is an attempt to reduce burden at the expense of, you know, protections and those people will be listened to equally to -- to those people who are making an effort or at least

interested in reducing burden.

I think -- you know, I think I said in my earlier -- my earlier general statement, and I repeat it again, that always, always we are looking for the balance between protecting the subjects and allowing important research that has public benefit to move forward but it is -- there is a balance and we will not be dealing with this report in an unbalanced way any more than we would in, you know, changes to human subjects protections.

PROF. CAPRON: And has this been a topic of discussion in the Human Subjects Subcommittee of the Science and Technology Council?

DR. SKIRBOLL: That I do not know.

PROF. CAPRON: No.

PROF. CHARO: Dr. Scott-Jones?

DR. SCOTT-JONES: I was intrigued by the comment, I think it was from Dr. Skirboll, about there being perhaps too much regulation and not enough guidance, and also I was thinking about the need for researchers to internalize basic values regarding the treatment of research participants so that their decisions in their own every day work rely not only on these regulations but on their values regarding the treatment of research participants.

I was wondering given your recognition of the

need for more guidance and more discussion of these issues, do you make efforts to connect with the professional societies that are dealing with these issues? For example, the American Psychological Association, the Society for Research and Child Development, all have committees that deal with these issues. The Society for Adolescent Medicine has worked on issues of adolescence in their treatment and research. Also, graduate training programs get concerned about this. Commissioner Backlar has told us about an effort she is involved in to train citizen or community members of IRB's.

So what efforts do you make to connect to these other elements in this overall process of conducting research where these issues are being discussed?

DR. SKIRBOLL: There is a lot that goes on at NIH in that regard. Each institute, the National Institute of Mental Health, the National Institute of Child Health, works with various societies in developing their own guidance. Many of the societies have their own guidance and ask for advice from the National Institutes of Health about putting together that guidance.

In some cases we put guidance out. We put guidance out not only to our investigators but some

institutes have guidance out for research participants. What questions should you ask when you go into a research protocol?

There is a lot of diverse, and in this case necessarily diverse, efforts.

You will note that NIH put up recently on its web some guidance with -- for IRB's in dealing with patients that have some degree of decisional impairment. Again not a change in regulation but some guidance of how IRB's should consider dealing with such patients.

We have a new -- we have a new booklet we are putting out on guide to the perplexed with regard to how to handle stored tissue, which is again guidance for investigators in how they view stored tissue. What is stored tissue in terms of human subjects? NCI has put together a group and it is now an NIH-wide document. So there is an enormous amount of activity.

Increasing, again, as the research gets more complex. We are about to put out a set of principles on privacy and confidentiality on research records which we expect to disseminate not only to policy makers but to our investigators so they understand what are the underlying principles of privacy with regard to handling research information.

So I like to think we are pretty responsive

in that. There is never enough.

PROF. CHARO: Jim, did you want to respond to this question?

DR. SHELTON: Yes. I think the general point looking through this issue through a human behavioral lens, in addition to a rather than a regulatory lens, is really, you know, potentially very fruitful and the idea of guidance and education and professional societies. If you want a social norm to occur you should be thinking about the ways to promote a social norm over and above the regulatory approach.

PROF. CHARO: Dr. Miike? Mr. Holtzman?

DR. HOLTZMAN: Thank you. Dr. Skirboll's comment about the confidentiality issues takes place against the backdrop of we have pending legislation dealing with medical records confidentiality and something we confronted in our tissue report was the issue of exemption from the Common Rule if information was encrypted.

And in one of the handouts today to us from the -- called "How to Interpret the Federal Policy for the Protection of Human Subjects," it says specifically that research would remain exempt if the investigator had access to identifiable information thus legitimate encryption renders research on such information exempt.

I was just curious around this table, getting to issues of consistency, how each of the people -- agencies reviews encrypted information? Whether the existence of encryption shielding the investigator from the identity of the subject renders it exempt. You can just all go around and say yes or no.

DR. SPEERS: We consider encrypted information to be coded and, therefore identifiable and it would not be exempt, and I am going to say in most cases. The reason I want to say that is the one situation that might be different is where the assurance of confidentiality that CDC has under Public Law 308(D) might change that situation.

DR. McCORMICK: We have a provision that is in our NASA policy directive but I think I hope I understand the interpretation of the word "encrypted" because this is a new field for me so I am not sure I am using your term correctly but we have a paragraph that talks about the fact that research activities involving the collection or study of existing data, documents, records, pathologic or diagnostic specimens are exempt from this MPD if these sources are public or available or if the information is recorded in such a manner that subjects cannot be identified.

DR. HOLTZMAN: That is the reg. The question

is the interpretation of the reg.

DR. McCORMICK: Well, we have had a couple -- we tend to use that -- we tend to use that exemption, that ability to do the exemption, and obviously generally speaking we are working with human subjects, and you can imagine in situations such as our recent experience with Senator Glenn it is a little difficult to keep his data confidential since he kind of appears 3 sigma out in much of the data that we have collected on him.

DR. CORTESI: We at EPA in coping with that issue have basically not run into an issue where it would have hurt the reputation or subject the subject to criminal, civil questioning, so -- causing (sic) fine has not arisen in EPA yet.

DR. SKIRBOLL: I think NIH has stated in documents to you that we consider coded information identifiable and not exempt.

DR. LEVIN: I think we would feel the same. It would have to be really tissue -- I mean, we have a dental institute that works with us and some of these people go around and collect extracted teeth that the dentists keep in buckets. There is no way that the dentist could know who gave that particular tooth and there is no way that our scientists would know where that tooth came from. They are just looking at adhesives,

dental fillings, et cetera, on human teeth. In that case, you know, it is an exempt situation and there is no way to go back to the original donor.

In the case where the original donor is known but they have coded the information that would not necessarily be exempt.

DR. PLATTNER: I simply have no experience with encrypted so I have nothing to say. I am sorry.

DR. SHELTON: No. I think the real question is whether it should be exempt. That is what you really -- we all really ought to be thinking about.

DR. HOLTZMAN: No. Actually I was interested in how it is --

DR. SHELTON: I know.

DR. HOLTZMAN: -- being -- and particularly gave you the question --

DR. SHELTON: I know.

DR. HOLTZMAN: -- whose serves on this working group?

PROF. CHARO: As a matter of fact, Dr. Shelton was the author of that document in front of you.

DR. SHELTON: As you may know, this particular part of the Common Rule is, I would say, the most difficult. It depends on the word "readily" and

what -- you know, what is subordinate. It sort of is the subordination of logical flow that you get to that and whether the word "readily" modifies ascertainable, which is in the next clause, or not.

DR. HOLTZMAN: Okay.

DR. SHELTON: So as I read that, yes, because the word "readily" does modify it that would be exempt.

DR. HOLTZMAN: But to me the real question is should it be.

DR. RODRIGUEZ: At the Department of Education --

DR. HOLTZMAN: That is enough.

PROF. CHARO: Right. We have descended into the depths of grammar, I think.

(Simultaneous discussion.)

PROF. CHARO: We have -- I am sorry. You wanted to respond, Jim. I am sorry.

DR. SHELTON: Well, I wanted to respond to something else.

PROF. CHARO: Oh, Ms. Rodriguez. I am sorry.

DR. RODRIGUEZ: I just wanted to comment that the Department of Education, how our use of encryption then follows education statistics on our implementation of the privacy act but then there are certain outliers when you look at quantitative data like that that you

know who the case would be. So in our case it is not necessarily exempt.

PROF. CHARO: Rhetaugh, did you have a hand up earlier?

DR. DUMAS: I did a long time ago and --

PROF. CHARO: I am sorry it took so long to get to you.

DR. DUMAS: Well, I think I will pass. I have been pondering this whole issue of the balance between flexibility -- I like that term better diversity. I think in this situation diversity is not a virtue and we need some commonalities. I think that is probably the reason for the Common Rule. But I will just pass.

PROF. CHARO: I know that Drs. Speers and Dr. Plattner wanted to make a couple of comments, and as we have run out of time what I would like to do is ask one question of my own and then everybody a chance to respond to anything they have heard, including what you already had planned to say.

One of the issues that has not been touched on much has been the question of interagency coordination when there is overlapping jurisdiction. For example, where EPA, USDA and OSHA might all have a role in supervising the circumstances surrounding research with new pesticides that are being applied in fields by

farmworkers. And I know that Dr. Rose quite a long time ago once talked to me about similar situations between OSHA and the Department of Energy having overlapping roles in certain research settings.

I would be interested as you complete your thoughts here for the moment, at least, and please do send in any additional information that occurs to you after the meeting, to what extent the current system is functioning well or functioning poorly at making sure that human subjects in these kinds of overlapping settings are being well protected and at the same time that the agency officials are not spending more time than is needed in order to achieve that good protection.

Let me just let you all go around. I will start with Dr. Speers since she had her hand up earlier.

DR. SPEERS: We have several examples where CDC has collaborated with other federal agencies. We currently have a collaboration with the Department of Education. We have others with the Department of Justice. We have long-term collaborations with USAID.

What has happened in these situations in recent time is that in order for CDC to collaborate, the federal regulations need to be followed and what that means is -- particularly if we are working with an agency that is under the Common Rule so they are under subpart

A, it actually brings then the subject -- the study, I am sorry, is reviewed under all of the federal regulations. And two particular cases, one with children subpart D was applied, and in the case of prisoners subpart C was invoked for the review of that project.

It takes time to do that because, in part, what we have to work out is the agencies have to work out and agree how the project is going to be reviewed and who is going to review it, and it takes time for that collaboration to take place.

It is actually easier when it is at the agency level because then we have agency officials that are involved in the negotiations and in the review. It becomes more difficult when there is an outside, a third party outside, involved in it.

This is a particular case that I am thinking of: In some of our international research where we are working with USAID and perhaps a Ministry of Health in a foreign country is involved. USAID has been working with the Ministry and has negotiated a set of requirements for the study.

CDC comes in behind USAID to actually carry out the research and we come in some time later and introduce a whole other set of requirements and often in that situation that third party is caught in between two

federal agencies that have different requirements and then we have to resolve those requirements.

PROF. CHARO: Others who --

DR. CORTESI: We at EPA have done work with H2S (sic) and this and that and there has basically been no problem. I mean, you get together and decide who is --

PROF. CHARO: H2S meaning HSS?

DR. CORTESI: Yes.

PROF. CHARO: Sorry.

(Laughter.)

PROF. CHARO: I must have the old --

(Simultaneous discussion.)

DR. _____: You still think of it as HEW.

PROF. CHARO: That is right.

(Laughter.)

PROF. CHARO: Okay. Dr. Levin, Dr. Shelton, Dr. Gerrity and Dr. Plattner, do you still want to speak to this? You kind of had dibs on next spot.

DR. PLATTNER: Well, I do not know how helpful this comment will be but as I think about these things and talk to colleagues and other people involved in human subjects I am always struck by the difference, I think, in personality or in general approach to these

issues. And this is my current understanding of that difference: Some of us -- that is me, I am on this side -- are very concerned about minimizing the risk and if there is no risk we are going to let the thing go forward.

And others of us, just as professional, just as, you know, accomplished, just as good in every way are very concerned about consistency in regulations, and that tension between the person who says, "Yes, but you cannot do this because the regulation does not say that," and the other person, and I am the other person, who says, "Let's not worry so much about the regulations. Let's look at what the actuality is and if there is no risk let's let the thing go forward. Let's not enshrine regulation just because it is there."

So that is my comment.

PROF. CHARO: Dr. Levin?

DR. LEVIN: Talking about interagency coordination, I think in most cases this tends to work well but we did have one situation where a number of different agencies were going to fund a particular research project that was actually being done, I think, at a university. And when we -- and everybody, I guess, was reviewing this separately and when the NIST IRB looked at it we found a number of issues which I brought

to the people who were planning to fund this, and based on the issues that we brought up they -- NIST decided not to go ahead and fund this research.

But my understanding is, and I did not really follow it any further because we were out of the loop at that point, that the research did go forward and that the other agencies did fund it. So this is this difference between maybe some people who take a less stringent view of what was happening and other people who, you know, look at it from a different point of view.

But there was no interaction in a sense between the NIST IRB and whoever else had reviewed this. The interaction at NIST was with the people who were going to fund it and when we told them that we thought there were some real problems with the science and the risk involved we just dropped out of it.

I do not know how one handles this. You know, and then the project, I think, did go forward.

PROF. CHARO: Dr. Shelton?

DR. SHELTON: Just one that one issue, I think here it is important to recognize really that there is an extremely large amount of consistency within the Common Rule. I mean, I find in dealing with colleagues a very high degree of consistency. Kind of like talking to a Canadian or something like that. I mean, basically it

is the same language with just a few little differences. It works pretty well.

PROF. CHARO: Dr. Gerrity?

DR. GERRITY: I just wanted to say that our general experience in VA with collaborative research with NIH and the Department of Defense, I think, has gone very well from, you know, the standpoint of the ethical conduct of research and have had very little disagreement.

I would like to comment, though, just briefly on what Dr. Plattner said. I think that --

PROF. CHARO: If I could ask you just to pull the mike just a little closer.

DR. GERRITY: Yes. I want to comment just on what Dr. Plattner had said, is that I think generally in our society we seem to have moved towards a view that it is not illegal, it is okay instead of really getting down to the basics of, you know, what is right and what is wrong, and not just what is codified.

PROF. CHARO: Dr. Rodriguez?

DR. RODRIGUEZ: Yes. In the interest again of the consistency, we in the Department of Education have engaged with HHS to work with us on the development of the tracking data system and database and that will certainly lend a lot of consistency as we work to

implement our work.

The other thing is that I think that there is -- if we look at our grantees, the Department of Education has benefitted a lot from the work that HHS has already done on the protection of human subjects, and many of the institutions that we fund and researchers also do work with HHS so they know the regulations, they know the policy, and are very helpful to our own program officers in implementing the regulations.

PROF. CHARO: I would like to thank you very much. Everybody was here far longer than they anticipated. I know that you all have offices to get back to.

DR. SHELTON: I thought you were going to give us a final comment.

PROF. CHARO: I thought that is what we just did.

DR. SHELTON: No. I thought that was specifically on the coordination issue.

PROF. CHARO: I am sorry. I was hoping to combine the two. It is a tough crowd. Feel free.

DR. SHELTON: May I make one?

PROF. CHARO: Yes, feel free.

DR. SHELTON: I just wanted to point out I ran across this actually last week from one of my

colleagues and it is an OMB publication entitled, "More Benefits, Fewer burdens: Creating a Regulatory System that Works for the American People."

I think this is some -- really it is really in the spirit of the kind of thing that I think we ought to be thinking about for this system because I think it is not a system that really currently -- currently it has some major strengths but it is really not doing this and there are some sort of subparts of this.

If I may just to get to kind of the diversity issue, I have not read it all but I did turn to a paragraph that says, "Employing Technology to Enhance Benefits and Reduce Burdens." There are lots of issues in this field but just one small one, if you follow them the lists are -- there is sort of an ongoing discussion about video conferencing for IRB's. Whether or not that should be allowed. Of course, the Common Rule does not really address that at least as I read it.

So we actually have one federal agency that currently, as I understand it, is saying no and one federal agency that is currently saying, yes, under certain circumstances.

And I do not know which one of them is right but I would simply point out to you that, you know, it is out of that of difference of opinion. It is

constructive. It is civilized. But that is one way you get to change in the way you do business.

PROF. CAPRON: And aren't they both in the same department?

DR. SHELTON: I would prefer not to answer that.

(Laughter.)

PROF. CHARO: Were there any other final -- yes, we have a comment from the audience. Dr. Ellis?

DR. ELLIS: My name is Gary Ellis from the Office for the Protection from Research Risk. There is absolutely no disagreement between the Food and Drug Administration and OPRR over whether IRB's can meet and effect a convened meeting by video conferencing. I do not want anyone to have that impression.

PROF. CHARO: Are there any other final comments from any of the people here from the various agencies and departments?

Yes, Dr. Speers?

DR. SPEERS: I will make this very brief. In one sense perhaps the federal agencies -- I will use the word -- might look a bit foolish because we appear to be inconsistent. What I would like to put on the table is that this is really a very complicated issue. Alex's question about a protocol going to three different

agencies and getting three different reviews, why would that happen.

I think it is really a very complicated issue and it -- and even though we come from the Federal Government and maybe should be one entity, in fact, we function and think and have corporate cultures of 16 or 17 different departments, and that is something that I think needs to be taken into account. I think you are hearing that, in part, where you are hearing about flexibility or diversity in interpretation.

But I think the agencies look at what is research and what is not research differently and legitimately. We look at level of risk differently and again legitimately. And I think that the commission if it can look at some of these broader issues would certainly help us in our attempt to try to protect human subjects.

Thank you.

PROF. CHARO: Thank you.

Dr. Shapiro?

DR. SHAPIRO: Thank you. First of all, I want to thank all the members of the panel for being here today, that is the visitors. I really very much appreciate and apologize for my own absence early in the session.

I just wanted to you indicated, as I indicated to my colleagues, I was not sleeping. I was, in fact, addressing a previous issue on mental disorders and issues of human subject protection, that area, at another place here in Washington. But I really want to thank you all very much for coming and I very much appreciate you taking the time.

I wanted to ask one question, and it came up when I was listening to this discussion, about universities having sort of different funders and have different rules and so on and so forth. The simple fact of the matter is that a -- in an extraordinary large number of research centers, university research centers, what HHS requires determines everything else because these centers are so dependent on funding from that source. That level of dependence is much, much greater than any other federal agency for most places.

I think as we think through these issues we should still have some understanding -- it is not to either explain or excuse any inadequacy on the university's parts or anybody, or agency's parts for that matter, but to understand that reality will help us form some kind of better ideas. That is -- I do not suggest we do anything about that but just suggest we observe it and take it into account when we try to develop whatever

recommendations we may.

PROF. CHARO: Well, then I am going to add my thanks to Dr. Shapiro's and allow people to finally take a break. We really do appreciate this kind of input. It is tremendously helpful.

Why don't we, on the commission, plan to reassemble in ten minutes at 10:30 when Dr. Moreno will begin a review of the comprehensive report and will be followed by some additional presentations at 11:00.

Thank you.

(Whereupon, a break was taken.)

DR. SHAPIRO: Let me say just a word about today's schedule for the members of the audience and commissioners alike. We will promptly at 11:00 o'clock because we have guests coming to speak to us, that is Nancy Dubler and Renee Landers will be here to speak to us, and I do not want to delay their participation in any way.

But we will turn in a moment to Jonathan Moreno to look at the outline of our Comprehensive System of Human Subjects Report and we will begin with that, and we will give Jonathan 15 minutes now and then we will turn to our guests, and if more time is needed Jonathan will return after that before lunch to deal with other aspects of things if we do not get through.

I apologize for the interruption.

My intention is that once we are through both a discussion of the Comprehensive Report and, of course, the report which are guests are going to give us at 11:00, to adjourn our meeting and use the time we have available this afternoon for commissioners to begin incorporating.

We will break up into either individuals and/or groups to just do some writing to incorporate some of the discussion we had yesterday to be able to give the staff more specific guidance as we go into the next version of the report, which as you know comes very, very soon. We are going to try to get another version out roughly in ten days and that will be the basis of our discussion at our meeting in Cambridge roughly 15 days from now.

So without any further comment, Jonathan, why don't we turn to you for the report on the comprehensive project.

OUTLINE OF COMPREHENSIVE SYSTEM OF HUMAN SUBJECTS PROTECTIONS REPORT

DR. MORENO: Thank you, Dr. Shapiro.

Over the past few weeks I have had the pleasure of reviewing a new genre of literature, namely that concerning the critique of the IRB system and to

some extent the Common Rule. It is not quite like reading Joyce but some themes do emerge, which I will talk about, uncharacteristically, briefly in the next few minutes.

I, also, have had the opportunity in a related genre to read, through the good auspices of Gary Ellis and Tom Puglisi, the last six years of OPRR decision letters, which develop some of the same themes of concern and so I will be able to interpolate that experience as well into my little summary in the next few minutes.

But I begin with a reminder to myself, I guess, as much as to the commission that the commission has already spoken in a broad sense with regard to the Common Rule and the IRB system when it resolved a little over two years and one month ago that "no person in the United States should be enrolled in research without the twin protections of informed consent by an authorized person and independent review of the risks and benefits of the research."

Now that resolution, which was subsequently echoed, should I say, or conjoined by the president in his speech that he gave at Morgan State University only one day later, raises as many questions as it answers for the purposes of this report.

For example, what implications does that resolution on the part of the commission and that position on the part of the president have for privately funded research as was mentioned this morning, for the extension of the Common Rule, which turns out even in its currently not to be perhaps so common, to other federal agencies as was also discussed this morning, and finally, as I most hesitate to mention, what are the implications of that position that the commission and the president have taken for the states, the state-federal relationship with respect to state sponsored research and state regulated research.

These are large questions concerning the Common Rule that -- and the system of research that for the most part are not reflected in the genre of literature that I mentioned a few minutes ago but that might well need to be considered in this comprehensive report.

Well, during the past five years by my count there have been at least seven reports or reviews with various recommendations concerning particularly the IRB system. Most of them have tended to presuppose that something like the Common Rule is going to need to be in place. Perhaps without the depth of reform that my earlier comments have suggested.

Of these seven reports, six have come from the federal system. One from the Advisory Committee on Human Radiation Experiments, sometimes called the Bell Report, the OER report, which has given us the only hard data we have, incidently, so far as I can tell, on the nature, functions and actual practices of local IRB's.

The GAO report, DHHS Inspector General report, NBAC's own report on persons with mental disorders who may be involved in research, and an academic group from the Center for Bieothics at Penn, and actually an interuniversity group that also published a report in JAMA a few months ago with which I was involved, and then in a somewhat different but related category the NIH's report on regulatory burdens.

I have just heard this morning that there is actually an eighth relevant document that now I need to read to extend my sophistication in this genre, namely the OMB's report, and I am very grateful to Jim Shelton for mentioning that.

In reviewing these documents and the decision letters, it seems to me that essentially one can create a list, and this is not by any means a lexically ordered list or an exclusive, mutually exclusive list, but there are essentially eight themes that one sees repetitively, several of which were mentioned this morning by the

agency representatives.

The first is that IRB resources are inadequate, at least for the busier research centers. Inadequate with respect to staffing in many cases, inadequate with respect to rewards for service on an IRB by professors, inadequate with regard to initial and continuing education of IRB members, and perhaps of investigators themselves.

So the first concern is inadequate IRB resources. The second concern that emerges repeatedly through these reports is that multisite trials are hard to oversee. IRB's often are confronted with a single consent form that they would like to revise in light of local conditions, which is supposed to be one of the virtues of the local IRB system but they are told that if they revise the consent form that their local investigators are out of the picture because that would skew the research, it would distort the process of recruitment, the admission of subjects and so forth.

Another concern that has been raised with respect to multicenter trials is that -- this is an example of the kind of problems that have been reported -- is that IRB's do not know what to make of adverse event reports that come from off site. They do not have the resources in many cases even to follow-up as effectively

or as clearly as they would like concerning adverse event reports on site but when they have off site AER's then they really feel that they have been given information that puts them in a very awkward position and they really do not know what to do about it.

A third area that comes up again and again in these reports and documents is the lack of routine on site monitoring of study procedures. The way, for example, that consent processes actually work. IRB's, of course, according to the regulations have the option of engaging in on site monitoring if they wish in situ but, in fact, this seems rarely to take place as many of these reports have asserted.

The fourth area of concern one sees again and again, the fourth theme is that certain regulatory requirements are particularly burdensome or inconvenient. Continuing review, rules concerning continuing review is one that one sees. Rules concerning annual reports. There certainly has been some adjustment there apparently at NIH but that again is an area of repeated concern.

So the burdensomeness of certain specific regulatory requirements, in particular those concerning annual and continuing review is often mentioned.

A fifth theme is that IRB's often feel that they have a lack of information, that they are just in

the dark. The only information they get is either formally through the protocols, the paperwork that they get from the investigators, or informal information that they might have about the conduct and competence and thoroughness of investigators with respect to research risks and informed consent that they happen to know because they are colleagues.

In particular, one sees mentioned that IRB's are not routinely aware and would like to know if the FDA has ever sanctioned an investigator in their institution. They are unaware of investigator's potential conflicts of interest. Sometimes that lack of awareness, of course, is much to be desired perhaps because it is not clear what kinds of steps and under what conditions IRB's would be able to take measures concerning investigator's conflicts of interest but they do not know about them so it is a mute question.

They also do not know about previous IRB reviews of a certain protocol thus enhancing the suspicion that a degree of IRB shopping takes place.

And, finally, IRB's are not privy to the reports that are filed by Data Safety and Monitoring Boards when those boards exist and there is a question about whether they should have access to those reports as sensitive and as confidential as they are supposed to be.

Nonetheless, one sees in these reports and these reviews of the system concerns expressed about the fact that IRB's are in the dark with regard to data that DSMV's collect that may be relevant to the assessment of a continuing review, for example, of a project by the IRB.

The sixth area, which has surfaced, I think, very briefly this morning also is that there are differences in NIH and FDA approaches to regulation. Not even perhaps so much the way that the words appear on paper, the compliance itself is not even, I think, the primary concern that is expressed. It is rather that the approaches, the attitudes, the portions that the FDA and the NIH are concerned about are different, and the cultures of the oversight agencies are different, and this causes at least some prefloating anxiety on the IRB if not -- if not a specific contradiction between the way the agencies approach their work.

Seventh, one sees various attempts in these reports to develop a concept that goes beyond the NPA/SPA system with respect to knowing where the IRB's are and who is on them, how many there are, and how many subjects, how many human subjects are actually being utilized, and how frequently.

For example, repetition -- repetitious use of normal subjects as well as people who are sick. Those

are all -- that is all data that we do not have for the most part and once these various theories in these reports about how to get that kind of information -- a couple of the reports recommend that all IRB's be registered, for example, going beyond the fact that there is, of course, a centralized MPA/SPA list.

More recently there have been moves, as you probably know, in the research community through organizations like PRIMER and ARENA to develop a certification process for IRB members and perhaps even some kind of quasi-public-private accreditation process or licensing for institutions that have IRB's. I am sure you will be hearing more about this over the next few months.

Finally, one sees in these reports, as one has heard this morning, also that perhaps it would be useful to have a central body to deal with novel or especially sensitive or especially complex, especially exotic research areas. It would help to give guidance to the local IRB's.

Some of these models, specifically perhaps with respect to genetics are already in place, but one often sees in doing this kind of meta-analysis of the reports that have been produced in the last half dozen years, one often sees reference to the need for some kind

of more centralized development of guidelines for emerging research areas or research that involves vulnerable populations.

I will end there and look forward to any comments and suggestions. Thank you.

DR. SHAPIRO: Thank you very much.

DR. MORENO: Alta, did you -- I am sorry. Alta and I had closeted yesterday to talk about some of these ideas as well. I just wanted to make sure I had not forgotten anything.

DR. SHAPIRO: Alta, has Jonathan forgotten anything?

PROF. CHARO: No.

DR. SHAPIRO: You have forgotten together whatever has been left out so far.

Thank you very much and thank you for summarizing that in a very coherent and, if I may say so, appropriate way. But let's see what questions there are. We have perhaps five minutes for any further questions or observations regarding other aspects of this. Of course, it reaches -- the report reaches farther than has just been indicated. And then if there are still further questions after that we can take them up later in the morning.

Alex?

PROF. CAPRON: One question about the presentation that is outlined for us -- is that appropriate now?

DR. SHAPIRO: Absolutely.

PROF. CAPRON: Okay. It seemed to me that while the organization that you have sketched here is straight forward and in many ways an understandable way to present things.

The separation of the various topics according to the current system and then possible changes means that given the wide variety of things we are going to be talking about it is possible, it seems to me, that people wanting to think about any particular topic are going to find themselves flipping back and forth between chapter two and three.

And I would just invite you as you begin working this up further to think about grouping topics and not having a report which is simply the current situation in whatever length or variety of topics and then the proposed changes but rather those topics which come closest together.

Now obviously there could still be a briefer statement of the current situation with an overall description but then once one goes into, well, why is the current situation vis-a-vis the placement in OPRR, the

amount of information variable to IRB's, interagency coordination on projects that are multiple, et cetera, that those might usefully be presented, problems, suggested solutions in tandem, and whether that means we have a dozen smaller chapters or one chapter that goes through A, B, A, B.

DR. MORENO: I have been working -- I think that is well taken and I have been thinking about that, too. Not to extend the structural analogy with Joyce but there is a geography of documents and one needs to be aware of when one is developing them.

I have been working mostly from an outline or based on an outline that was developed last fall when I was not around but -- and I think one way to deal with this problem might also be to pay -- spend some time thematically in the chapter on conclusions and recommendations, that is to say to tie together the description of the current system, its difficulties and so forth, with proposals for change. So that might be accomplished in that last chapter but I take the point.

PROF. CAPRON: Now if I could comment on two topics that are not specifically, as I see it, addressed here and maybe it is in the interstices and it is here, and obviously there are a lot of smaller topics, Jonathan, which your current review indicate need

attention and description as weaknesses that are not on the list of weaknesses here.

DR. MORENO: Yes.

PROF. CAPRON: And I am sure you will be adding those.

The two topics are the question of the assurance model versus the FDA inspection model, and you have mentioned that obliquely and mentioned the thought that some private organizations are putting forward of an accreditation model.

I would urge the commission as a whole to read the relevant portions of the 1983 Second Biennial Report on Human Subjects Regulation from the President's Commission. That report recounts the limited pilot study that the President's Commission did of a peer based inspection model.

In other words, it took the idea that the FDA had, which is it is helpful to go out into the field and look at what is happening. As I understand it, the FDA in its process, at least at that time, used people who were -- people who had many responsibilities for different types of inspection by the FDA and their major process seemed to be a sort of follow the paper trail process. I mean, if you had a sponsored research that had gone through the process, make sure that the relevant

papers had been filled out and so forth.

The President's Commission thought it was valuable to consider a process which instead of using or primarily relying on these FDA expenditures would use people from other institutions with comparable experience, both allowing some cross fertilization but also having people with in-depth experience in the field, which is very close to the accreditation model that is used elsewhere. Educators inspect other educational institutions; hospital administrators, physicians and nurses survey hospitals for the Joint Commission and so forth.

I would like to see us return to that topic and it seems to me this is the place to do it. How does that mesh with or would it modify the assurance model?

The second question is what do we do with the international project and to what extent, Mr. Chairman, is the timing of this report such that you would be concerned that its timing would be affected waiting for the international versus having something that is less complete because it is one of the branches of human subjects protection that we are looking at. And I just wondered if there had been any discussion within the executive chamber of this commission about that.

DR. SHAPIRO: If there had been an executive

chamber I had not recognized it yet but in any case that is an issue we are concerned with and it really depends a little bit on the progress we make this summer on both of these projects and so we will just watch it as we go along.

PROF. CAPRON: In theory, if it were possible to have them working in tandem, wouldn't the idea of a report which took into account -- many of the issues that we are looking at in the international area are the same or closely related to the issues of coordination, consistency, interpretation of the regulations.

DR. MORENO: Eric and I actually talked about that and we have agreed that Ruth Macklin and I will talk

PROF. CAPRON: The office is not so large that you cannot have communication between you and Ruth Macklin.

DR. SHAPIRO: This is an important issue. We have to really work it out.

DR. MESLIN: The only thing I would add is that both Dr. Moreno and Dr. Macklin, who is also a part-time staff member with us, are physically sharing the same office at NBAC so that will encourage coordination and communication between them.

DR. MORENO: And infection.

(Laughter.)

DR. MESLIN: But the --

DR. MORENO: We are not going there.

DR. MESLIN: -- the other more relevant issue is that we will be having a full discussion of the international project at the July meeting in Cambridge, the second day of that meeting, so you may have a better sense and the commissioners may have a better sense within the next 15 days just how far along they are and how much work they need to go. But I know that Ruth is very aware of this issue as well.

DR. SHAPIRO: Alta, and then we are going to go to our next subject and revisit this later on this morning.

PROF. CHARO: I would like to add on that, Alex, that I was able to attend the meeting last week at the Fogarty Center on international norms in research, an invitation that must have come through the commission, and as a result there is a lot of material that was presented there that is now available to us and a lot of discussion that will be reported back, and I will be happy to share the, you know, kind of summary of the meeting.

That can serve as a fairly extensive placeholder, including a placeholder on key topics like whether there is a subset of specialized areas of

research that would benefit from the existence of a national review body that picks up topics that IRB's themselves --

DR. SHAPIRO: I am interested in this answer.

PROF. CHARO: Okay. That IRB's themselves cannot handle because they see them so infrequently so I do not think we need to worry this report will get held up. There is enough material available.

DR. SHAPIRO: Thank you. I would like to see a summary of that meeting if it is easily available.

PROF. CHARO: I will provide it for you.

DR. SHAPIRO: It will be very helpful.

Jonathan, apologies.

Let's suspend this part of the discussion now because I do want to move to the report. It is a mouthful but it is a Report to the Advisory Committee to the Director, NIH, from the Office for Protection from Research Risks Review Panel. It is the OPRR issue that we have thought about and I want to welcome both Nancy Dubler and Renee Landers here.

Thank you both very much for coming. I know it was a trip for you and it is a great pleasure to have you here.

Thank you very much. The floor is your's.

REPORT TO THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH,

FROM THE OFFICE FOR PROTECTION

FROM RESEARCH RISKS REVIEW PANEL

DR. DUBLER: Shall we begin?

DR. SHAPIRO: You should begin.

DR. DUBLER: My name is Nancy Dubler and thank you very much for inviting us to be here today. We were asked by the NIH to do a report which would look at two particular issues.

(Slide.)

One, to ensure that the organizational locus at the OPRR continues to be the most appropriate for OPRR's mission and future directions of research. And, two, to advise whether there is a need for OPRR to have additional delegated authority to accomplish its mission. Those are relatively narrow tasks we were asked to address by Dr. Varmus.

(Slide.)

The members of this task force were, in fact, a very interesting and knowledgeable group. They included myself and Renee Landers, who will complete the presentation, Barouche Brody, Ralph Dell, Ruth Macklin, June Osborn.

(Slide.)

This committee heard a number of people both from within the NIH and without discuss the issues of the

present function of OPRR and the possible benefits or detriments to that office's function were it to be moved.

(Slide.)

We have organized our report into a background session and then a particular set of recommendations. I will begin with the background and the first recommendation and then Renee will then finish the discussion.

(Slide.)

Even though our charge was a relatively narrow one, the committee members felt that it was appropriate to address the functioning of OPRR in the context of research and in the changing nature of research, and the changing problems that appear as research becomes increasingly multinational, complex, and funded in decreasing amounts by the federal government, and increasingly by private industry.

Therefore, we talked about the nature of research at the outset and emphasized the fact that at the time that the federal regulations and OPRR were created for governing research the focus was very, very much on the risks that research presented. There has been a shift certainly in the last year to emphasize not only the risks but the benefits and, therefore, that research has become a much more integral part of the

medical scientific establishment.

Concerns about human subjects are growing and are increasingly part of the news. We do not specifically mention in our report but for those of you who have not followed the very interesting New York Times set of articles on problems in research they are very interesting and they are very public, and they highlight some of the issues now involving human subjects.

Certainly your own report on research involving subjects with mental disorders that may affect decision making capacity has raised in the scientific community and again in the public the issue of the involvement of subjects in research and the possible benefit to them and the risks to them from that involvement.

The President's discussion of the Tuskegee research and the human radiation experiments have also brought to the public attention the fact that research is, in fact, involving many human subjects who may benefit or be harmed.

The question now is the question of OPRR in protecting human subjects and OPRR has been asked to play a very key role in how we think about and regulate research. There is the perception, the committee found, that OPRR because of its place within the NIH hierarchy

may be biased toward research and, therefore, provide insufficient protection to human research subjects.

With respect to ethical issues raised in connection with biomedical or behavioral research involving human subjects, OPRR is key in providing guidance to IRB's and to researchers who are designing research when they have questions about their ability to include human subjects or about their obligation to protect them.

Certainly OPRR is very involved in the formal written assurance process which all institutions which receive funds from the federal government must complete and be in compliance with.

OPRR also is very involved in the welfare of animals involved in research. Both the USDA and the Department of Health and Human Services are involved in the protection of animals. The Public Health Service policy on humane care and the use of laboratory animals is the law that governs both departments.

The USDA and the DHHS, that is OPRR, approach regulation involving animals quite differently. The USDA relies upon on site inspections by veterinary medical officers. Whereas the Department of Health and Human Services relies more on the education and training of researchers which is conducted by the Division of Animal

Welfare. The Division of Animal Welfare is administered entirely by board certified laboratory animal veterinarians.

Now, in theory, the public health policy extends to other agencies. However, the Division of Animal Welfare within OPRR has probably been less involved in the work of other agencies than would be required by a broad commitment to animal welfare.

The subject of justice and fairness in research is an important one. Increasingly, as HIV infection is perhaps a good example, HIV infection raised for many possible participants and human subjects research the issue of not only their protection from that research but their desire for access to that research.

So the desire on the part of HIV infected persons and the families and those afflicted with Alzheimer's disease, for example, for access to research, the growing debate that I know your commission is involved in about either expanding or reinterpreting the regulations involving children in research. All of these are areas in which OPRR eventually will need to provide leadership, guidance and education to IRB's and human subjects researchers.

The committee also identified the task force's concerns about nonfederally funded research. As

federal funds, over which OPRR has aegis as those funds are expended by institutions under an IRB process, the issue of whether nonfederally funded research will be subject to comparable rules is an interesting question. And whether OPRR will then be in a position should that be the case to interpret those rules and exert moral leadership within the research community becomes quite important.

The dangers of concurrent state and local regulation, we had in this section of the report a discussion of "the Balkenization" of research. We removed that particular word at the very end and talked about the fragmentation of research. It seemed more sensitive to the times. But I will give you two examples which I am sure you know.

The State of Maryland recently rejected but seriously considered research that would govern -- regulations that would govern research with the mentally infirmed. New York State, as Jonathan knows, he and I have been involved in a committee, which I chaired, which looked at research with normal healthy volunteers.

That report, which will eventually come out, Jonathan, suggests guidelines for the state to use, not new regulation, but I am, in fact, beginning to chair a committee in New York State in September, which is going

to look at research with children and there is a great debate in the state as to whether these should be regulations layered upon the federal regulations or these should, indeed, be guidelines.

You spoke a little bit, Jonathan, in your last comments on the difficulty of multi-institutional research. Well, consider multi-institutional research which need not only worry about the informed consent document and process but which has to deal with a whole different set of regulations.

All of these example are by way of saying that issues in research are becoming increasingly important and many issues will require the leadership of OPRR as we go ahead.

And that brings me to our first recommendation:

(Slide.)

We recommended that OPRR should be administratively relocated from its present location within the NIH. OPRR is not perceived as an independent office. It is perceived as dependent upon and concerned primarily with research at the NIH.

The review panel concluded that relocating OPRR was the only way to address these perceptions and concerns and to ensure OPRR's independence and most

importantly to maximize its effectiveness.

The subparts of our discussion are the following:

One, there are conflicts of interest arising from OPRR's location within the NIH. OPRR is perceived to be affected by conflicts of interest. It is within a hierarchy in which it must concomitantly review research conducted by the NIH and regulate research conducted from the NIH.

The other departments within DHHS -- other divisions within DHHS and other departments within the Federal Government do not see NIH as equal in authority to other bodies and agencies from whom they take direction and receive education.

These concerns we concluded are neither abstract nor hypothetical. One of OPRR's obligations is to create a robust and productive dialogue within the agencies in government and we would hope that locating OPRR outside of the NIH should make it more willing rather than less to engage in consultation.

Secondly, concerns about conflicts of interest limit OPRR's influence within the NIH and this is a quite paradoxical situation but our sense from the people we spoke with is because OPRR is so concerned about actual conflicts of interest and perceptions of

conflict of interest it, in fact, has been excessively remote from some of the researchers at the NIH who have sought guidance and discussion about human subjects research.

Next, OPRR's location within the NIH compromises its effectiveness with entities outside of the NIH. The components within DHSS, the FDA and the CDC, for example, and the other departments within the Federal Government where OPRR is responsible for implementing the Common Rule do not acknowledge its authority. The CDC and the FDA think that they are equal or superior to this particular office and, therefore, that they are perfectly able to interpret the federal regulations on their own.

OPRR's subordinate position within the NIH does not foster or enhance its eminence with other departments or its connections with other agencies.

Next, oversight of OPRR is compromised by its location within the NIH. Because again the NIH is so aware of the perception of conflict and the actuality, and it was explained to us, for example, by OPRR that because of the present structure when OPRR has a suggestion for either regulatory change or interpretation which it would like to go to the Secretary that goes through a number of offices within the NIH and,

therefore, what arrives at the Secretary's office has, in fact, been edited and changed by the NIH process and OPRR argues dilutes its voice.

Because people are aware of that there were many within the NIH who felt that it was actually difficult to present sufficient supervision for OPRR and, therefore, that OPRR actually had too much authority without equally effective oversight. Hang on to your hat, I mean you probably could not see that one coming.

However, because of this perception of conflict and the actuality of conflict, people who were actually in a position to supervise the OPRR feel that they are hampered in their efforts to do so.

(Slide.)

The final point in this section, we did consider the fact that there are down sides to moving OPRR out of the NIH and how OPRR responds to that will be, of course, extremely important.

In order to ensure OPRR's efficacy and independence after relocation three things need to happen:

One, OPRR needs to remain in touch with the research enterprise in developing research, must stay in touch with the culture of research, and must commit the time and attention to keeping up the connections that

will permit it to understand what is happening at the forefront and the edges of research and, therefore, there must be an intellectual commitment to being part of the research enterprise.

Also, let me state that moving OPRR outside of the NIH does not necessarily mean relocating its offices. The authority to supervise and the chain of command would not necessarily distance in the physical sense OPRR any more from the NIH than it is now.

Second is securing resources to support OPRR's mission and we are aware that being lodged somewhere deep down in the budget of the NIH is a very privileged position and moving the OPRR to any other place where it will be more visible and where perhaps some discussions will be seen as more controversial does open it up to the danger of having its resources scrutinized more carefully and perhaps compromised. That is, in fact, a problem.

How we -- how it gets dealt with is not clear to us or to the Secretary but there are a number of things I am sure that could be done. People commented with approval on the Genome Project that set aside a certain percentage of funds for bioethics research and perhaps agencies would have to be encouraged to do that and perhaps the NIH would have to continue funding it in

the same way it now does even if it does not supervise it in the same way.

Finally, insulating OPRR from inappropriate political influence is going to have to be a focus of the agency or person to whom OPRR reports. It does make it more politically vulnerable. As your last discussions about stem cell research here at NBAC have shown, these are very controversial issues, some of them, and on which politicians are likely to have some strong opinions.

OPRR will somehow have to be protected from those strong opinions.

So let me stop there and ask Renee to discuss the next set of recommendations and then we would be happy to discuss with NBAC any of the questions or comments that you have.

DR. LANDERS: Thank you.

(Slide.)

Nancy has explained the ways in which the location of OPRR within the NIH is perceived to limit on the one hand its ability to regulate NIH researchers and on the other hand it imposes constraints on NIH in supervising the activities of OPRR.

The review panel concluded, as you already know, that merely elevating OPRR within the NIH would not enhance the leadership role that it needs to have on

these issues. Therefore, the committee, the review panel recommended that OPRR should be located in the office of the Secretary of the Department of Health and Human Services and report either to the Surgeon General or to the Assistant Secretary for Health, which right at the moment is the same person.

And, also, we concluded that locating OPRR outside of the NIH would strengthen its ability to interact with other agencies within the Department of Health and Human Services and with other departments. Merely elevating OPRR in the NIH organizational chart, it did not seem to the members of the review panel that that act alone would not enhance OPRR's ability to exercise leadership within DHHS and with other federal agencies. While such a move might reduce actual impediments to OPRR's efficacy it would not eliminate the perception of a conflict of interest, which is part of the issue that the review panel thought that we needed to address.

OPRR, the review panel found, needs actual and perceived authority to achieve cooperation and compliance both within the Department of Health and Human Services and with other federal agencies that are subject to the Common Rule and the policy for the humane use and care of laboratory animals.

This is not just a superficial concern about

location on an organizational chart. I think that we all know that organizational placement signals the importance that the research community, the government and society attach to the work, and it is -- that burying OPRR in an unfamiliar bureaucracy, it does not signal to the public that the function is given the requisite importance and the importance that it deserves.

We also concluded that protections for human subjects and for the welfare of animals must be accorded a central value in order to maintain the credibility of science and by locating the office within the heart of the authority, and power, and stature of the Department of Health and Human Services, we thought that the government would signal that the concerns of OPRR, the concerns that OPRR deals with would have that central value.

It is important that OPRR's activities and concerns be accorded a central value because it is important to the credibility of science in order to sustain the public funding for scientific research and intellectual support for scientific research, protecting human subjects and animals is a key element of a stable research enterprise, and especially if OPRR shifts its focus as we also discuss in our report from emphasizing the assurance process to really actively -- more actively

engaging in education and training and exerting intellectual leadership.

The new location would afford OPRR greater flexibility and greater visibility and a greater ability to deal with other agencies and researchers on the issues that are of concern to OPRR.

(Slide.)

Our third recommendation was that the director of the office of OPRR should be a member of the Senior Executive Service, that OPRR in a relocated form would best be able to reap the benefits of the move if we enhance the stature of the person who leads the office. And in that vein we discuss in our report some of the criteria that the director of OPRR should have or some of the qualifications that the director of OPRR should have.

The director should have national stature in the scientific, ethics and legal communities, and the director should have substantial experience with issues of the design and conduct of research. A substantial knowledge about the complex scientific, ethical, legal and regulatory issues involved in research, and should have substantial interpersonal skills in order to be able to persuade others to follow the advice and guidance offered by the agency.

Finally, we thought that reclassifying this

position to the Senior Executive Service should provide an opportunity to achieve creative and strong leadership. The stature of the position would encourage and invite people who have leadership in the requisite fields to become interested in the position.

The idea here is to engender respect for the enterprise in which OPRR is engaged within the scholarly ethics community, the community of scientists whose activities are circumscribed by OPRR, and with the public. We also thought that enhancing the stature of the leadership of OPRR would be especially important again if OPRR shifts its focus from the largely ministerial tasks of managing the assurance process and really becomes more active -- takes a more active leadership role.

(Slide.)

We also acknowledge that a person would not be expert in all the areas that would be important for OPRR to have -- in which it would be important for OPRR to have expertise and we suggest that some careful thought be given to all of the OPRR staff because that staff collectively must possess a full range of expertise in science, ethics, and knowledge about the law that is relevant to the work that it performs.

(Slide.)

Next, we recommended that as part of the move of OPRR to a new location the Secretary should create an independent oversight committee, an advisory committee, to provide guidance to assist in setting standards and to review the operation of the office. We thought that this advisory committee could in a way respond to or compensate for some of the concerns or the perceived concerns that Nancy mentioned in her presentation that might be issues if OPRR is moved from NIH.

We thought that an advisory committee if properly structured could provide broader scientific and ethical resonance to discussions at OPRR. The composition of such an advisory committee should include scientists and ethicists, members of the public, persons who are knowledgeable about the protection of animals, and to bring a lot of different perspectives to the work of the advisory committee and to the work of OPRR.

This, also, would help maintain OPRR's understanding of the research enterprise and help keep it connected to what Nancy referred to and what we referred to in our report as the culture of research.

An advisory committee could offer ongoing counsel, comment and criticism about the operation of the office and help in examining -- for example, helping OPRR in examining the merits of a shift in focus from the

assurance process to some other type of activity. Such a committee could also react and respond to new ideas for regulation and for the protection of human subjects and the welfare of animals.

We heard many comments about informal guidance of OPRR that, you know, effectively become law that are issued without any kind of meaningful interaction with the scientific community, and the advisory committee could serve as a sounding board for those kinds of ideas before they are issued and promulgated.

A committee of experts could also help to ensure that OPRR is using its authority appropriately and creatively and can provide some barrier to the incursions of the political system. The advisory committee could serve as kind of a reasonableness check on the activities of OPRR and inject an element of discipline, review, rigor and an additional source of persuasive supervision of OPRR activities.

To the extent that OPRR's relocation would expose it to greater political intrusiveness, the advisory committee might be able to provide some additional insulation.

(Slide.

Finally, OPRR was asked to consider whether -

- the review panel -- excuse me. The review panel was asked to consider whether OPRR had adequate delegated authority to address the tasks presently assigned to it and the review panel concluded that, yes, the answer was yes, that for the tasks presently assigned to it OPRR does have sufficient delegated authority. It could go -- it could continue on the path it has been working on or it could go about its work in different ways but that its delegated authority would permit it to take a variety of options.

But we concluded that the resources available to OPRR may be inadequate fulfilling its mission. And this plea for resources probably will not distinguish our activities from the activities of any other similar kind of panel but we do think that additional resources are required if OPRR's role is to be conducted effectively.

Some critiques of the OPRR process, as Jonathan was mentioning in the presentation prior to our's, among the critics have been the Office of the Inspector General in a report that was issued last summer. These critiques question the effort and resources devoted to routine tasks at the expense of, you know, more proactive educational and ethical leadership activities.

And we sort of remain agnostic about how OPRR

should come down on what style of leadership it should exert but if its role is changed to a more active role, a proactive role, then more resources almost assuredly will be required and certainly if OPRR's delegated authority is changed in any way to include a broader range of activities, for example, regulation to privately funded research, that would include a vast expansion of OPRR's work load and require much more capacity and resources.

So we think that any new focus or any change in the style of activities of OPRR would require additional budgetary and personal resources to make OPRR more effective.

(Slide.)

Finally, Jonathan also spoke in his report about the need for leadership and guidance in this area, that to a certain extent IRB's are kind of left out to function in a world without a great deal of guidance and concern and effective advice.

We see relocating OPRR and focusing more on how it does its work in providing an advisory committee and effective staff for the office as an opportunity for federal leadership in this area.

The United States, as we mentioned in our report, is the unqualified leader in biomedical research and has played an important role in defining the ethical

standards for the conduct of research involving animals and human subjects. OPRR must lead and respond to the ethically compromised dual nature of research using individuals to the benefit to some degree of others and the resulting moral dilemmas that accompany the society's use of individuals in this way.

The concerns are heightened, as everyone is aware, for the mentally incapacitated and for children. OPRR plays a critical and could play a more critical and unique role in the ethical consciousness of the national research community but these responsibilities really require a more clearly independent office because research will become only more ethically complex in the future and even though the scientific advancement has resulted in the improvements in the prevention and treatment of disease and in the quality of life.

Some of these gains, regrettably, have been achieved at an unacceptable cost. And this unacceptable cost has created some public distrust of the research enterprise and that distrust really challenges the research community to convince people to continue participating in research and to continue funding research which is important to the stability and the future of science in this country.

So we think that with our recommendations and

a lot of effort on the part of good people within government and without that OPRR should be ready intellectually, morally and technically to lead the nation in the expansion of research within clear ethical pathways. It needs a staff, a stature, and high purpose, and it needs a position in the government that will give it the tools to achieve its potential in this area.

DR. SHAPIRO: Thank you both very much. First of all, on behalf of NBAC, let me express our gratitude to both of you for being here today and to you and your fellow committee members for a very interesting and I think extremely useful report.

This is a subject that we, ourselves, have visited at one time or another. And now speaking only for myself since I cannot speak for the commission, I find your report extremely useful and valuable and certainly moving us in an entirely appropriate and, indeed, necessary direction. So I am very grateful to you and I hope that many, if not all, your recommendations will be implemented.

Let me see if there are other members of the committee here who would like -- commission, who would like to ask some questions.

Alex, and then Alta.

PROF. CAPRON: To try to be to the point, I

have four questions for you. The first is how far up the process did you look? I mean, the thrust of what you are saying was that the authority, stature and effectiveness of the OPRR diminished because it is perceived by other departments and agencies as a subordinate division within HHS. How far up did you think you would go in that process?

DR. DUBLER: I do not understand the question, Alex.

PROF. CAPRON: Well, you went as far -- you have said, well, do not just move it up within NIH -- that is what Ms. Landers just was saying -- move it up to the Assistant Secretary level at HHS. Did you consider anything beyond that? To the Secretarial level, to the -- an independent level a la the Office of Government Ethics or any of the other cross cutting federal agencies that are not departmental based?

DR. LANDERS: We did actually consider some of those options.

PROF. CAPRON: But it really is not reflected in your report, is it?

DR. LANDERS: Right. I think that we have one sentence there somewhere that describes how we considered locating it in the Executive Office of the President, for example, as an independent agency. We

quickly rejected those options for a couple of reasons.

The independent agency route seemed to us to have all of the risks of moving OPRR out of NIH and none of the protections that the Office of the Secretary could provide for it. You know, you think of independent agencies like the State Justice Institute or something like that. They are very vulnerable in the budgetary process in the political process and we thought that that probably would not be a good situation to put this kind of activity in.

With regard to moving it up beyond sort of the Secretary level, I think the Secretary -- we tried to give the Secretary some flexibility in how she actually implements the recommendation about relocation. I think it would be possible for her to decide to have the person to report directly to her. A lot of people report directly to her now and we thought that it was not for us to say, you know, that another such report should be added to her work load.

But the Assistant Secretary for Health, the Surgeon General, have very powerful roles in the department and certainly from the perspective of the public the Surgeon General, you know, in the recent decades anyway has symbolized a kind of moral leadership on scientific and public health concerns that we thought

would in a way make the activities of OPRR -- would give credibility to the activities of OPRR.

PROF. CAPRON: The CDC, AHCPR and so forth, do they report to the Assistant Secretary for Health?

DR. LANDERS: No.

PROF. CAPRON: They have direct lines of authority?

DR. LANDERS: Although -- well, let's see --

PROF. CAPRON: The Assistant Secretary or the Surgeon General are in charge of funding that goes through the Public Health Service --

DR. LANDERS: That is right.

PROF. CAPRON: -- is that their part of the budget?

DR. LANDERS: That is correct.

PROF. CAPRON: To the extent that there is a perceived conflict of interest in having the office now a part of NIH and falling under the Director of NIH with both the levels of review and the sense that the person to whom they are reporting is under constant pressure from people in the research community whose funding depends on that person to hold back what are seen as additional or onerous rules or interpretations of rules vis-a-vis research, doesn't that same problem arise with the Assistant Secretary to the extent that that is also -

- that person's primary budget line is all the work that the Public Health Service does, all the money that flows into research?

DR. LANDERS: I am not sure that is entirely accurate but the way that we envision the process working is that by locating OPRR outside of NIH it removes the possibility that NIH would be able to effectively change, alter, to influence, you know, very specifically recommendations that come from OPRR before they reach the Secretary's desk.

Now it is true by keeping the office in the department, you know, that there are not -- there should not be rogue agencies in a well functioning department and any proposals by OPRR would still be subject to the departmental review process.

But our vision is that those proposals as they are developed by OPRR would be circulated unchanged within the department, which is not the case now that gets filtered -- filtered is the word I was looking for before -- through the NIH review process before it reaches that larger audience and we do not -- as we -- I think we suggest -- do not think OPRR should sort of operate independently without comment and review by knowledgeable people but we think it should take place at the departmental level and not have, you know, sort of a

screening process before the issues reached there.

PROF. CAPRON: My second question relates to the interagency coordination problem. The -- we were constantly in both of our prior reports -- excuse me, not both of them. Our Human Biologicals Material report, which has not come out yet, and our report on psychiatric research, being told that recommendations that we should make should somehow not or would be most effective if they did not require changes in the Common Rule. We heard a little bit about that this morning from several of the agency representatives.

At the same time that we are hearing the need to take into account developments in the field and the increasing complexity which you talk about, the notion that the present structure vis-a-vis the protection of human subjects is so complicated because the need to get agreement from separate departments and agencies is extremely -- poses an extremely great barrier to the necessary adjustments.

I wondered if you gave any thought -- because again I did not see any reflection of this in your report -- to where the location of the central office, the office with basic coordinating responsibilities, would be most effectively placed to overcome that problem. Again the question where in the federal structure? Did you

hear about that as a problem?

DR. DUBLER: We did. There were particular examples given by the FDA and the CDC where they thought their interests had not been well presented or represented given where OPRR is now in the structure of the NIH.

We did not consider moving it out of the Department of Health and Human Services to another department. That did not seem to make any sense given its responsibilities and the locus of most human subjects research within the Department of Health and Human Services.

Once we had rejected an independent agency the Nuclear Regulatory Commission suggested as one model and that did not seem to be very effective especially, as Renee said, because of the political and financial isolation that that independence would bring.

Once we thought about that we did not think it was a perfect solution to move it to the Office of the Assistant Secretary for Health, for example, but we thought it was the best solution available that would balance all of the tasks of OPRR.

Now specifically in relation to the Common Rule we had heard that, in fact, the Common Rule, which is quite important within the Department of Health and

Human Services is not as important and as central to the thinking in other departments and that, indeed, the greater visibility of OPRR higher up in this one department might permit it to exert leadership.

Now that does not go to one part of your question, Alex, which is if we change materially how we think about human subjects protection, do we have to go back and change the regulatory structure, and what are the political dangers in reopening that structure. We really did not focus on that issue but hoped that an OPRR that was more clearly independent that would be able to exert a moral and intellectual leadership within the national research community might, in fact, be able to achieve benefits which its present structure, funding and staff does not permit it to do.

DR. SHAPIRO: Last question, Alex.

PROF. CAPRON: Can I have one instead of two then?

DR. SHAPIRO: Just one short one.

PROF. CAPRON: Okay. It is very short. You have a section entitled "Dangers of Concurrent State and Local Regulation," and you give the examples of Maryland and New York, and saying that state variations in the requirements for informed consent and research conditions could be difficult to manage and you refer to

fragmentation.

Are you suggesting federal preemption in this area? And, if not, what difference does that issue make to this relocation of OPRR? I was just puzzled by those two pages or page-and-a-half.

DR. DUBLER: Right. We certainly have not suggested anything new in the debate over federal preemption. The role of the federal regulations in research and how they are regarded by state health agencies, number one, by institutions and by researchers is a discussion that has been going on for some time. We are suggesting it is getting more complicated and that, in fact, we are not suggesting federal preemption but we are suggesting again that an office with enhanced moral and intellectual authority and position might be able to help broker and negotiate more of a uniform intellectual community over the next years.

DR. SHAPIRO: Thank you very much.

Alta?

PROF. CHARO: I would like to understand better how current functions of OPRR as well as some additional functions I think you were identifying would be distributed in the new format that was suggested. When I think about these functions they include advice as well as education, advice on a protocol by protocol basis

or as issues arise as well as, you know, kind of formal education, compliance enforcement and policy making.

Your advisory committee, I am trying to understand exactly what the model would be, I am thinking in terms of things like the advisory committee to the Director of NIH or a Board of Directors is what I am imagining -- please correct me if I am wrong -- in terms of how it relates to the office.

DR. DUBLER: Board of directors, you mean the advisory committee we suggested?

PROF. CHARO: I am trying to understand exactly how the advisory committee that you have suggested would relate to the new office and the models I am keeping in mind so I would like to know if they are correct are a corporate board of directors or the ACD for Harold Varmus. I gather would play the role of, for example, looking at novel interpretations or evolving interpretations of regulations or development of ideas for new areas for interagency cooperation. The office would handle both compliance and education.

I have heard some people suggest that the combination of education and enforcement poses some difficulty on the part of researchers and the local IRB's because it can create a chilling environment when an IRB wants to check out something, whether it is -- whether we

need to be reporting a violation, is it serious, is it continuing, or some other aspect of IRB operations. There is some nervousness that asking for advice opens them up to some degree of enforcement action. I wonder how much you thought about these two particular roles continuing to be grouped there.

With regard to the policy making I was wondering how that would play out with the existing interagency task force and regulatory reform processes that are involved in notice and comment on rule making. What is the plan for what and how will they be organized?

DR. DUBLER: Let me just open this and then ask Renee to comment also.

We felt that an advisory committee probably closer to the ACD than to any other model that would hear what is going on. Review, for example, an enforcement action that closed down the research at a particular institution and say we think that was interesting, useful, appropriate, too precipitous. A discussion of how the office was, in fact, working, the sorts of advice they were giving, whether that advice really does reflect the best thinking that we can put together on the very complex issues of law and ethics and regulation in research.

The policy making obviously would become more

public than it is now with an advisory committee and we hope more responsive to what are growing rather than diminishing problems in how to think about human protection on the one hand and the benefits of research on the other.

DR. LANDERS: On the part of your question that dealt with the different roles, the advice giving role, the consultative role, the enforcement role, that is a problem inherent in almost every regulatory structure. The -- I used to teach administrative law in a former life and it is one of the great conflicts.

I think that we envision OPRR's role and effective regulation in this area to be regulation that uses enforcement as a tool only as a last resort. That by really effective education and training and interaction with the research community, getting compliance up front is a better way to go than to try to use a kind of prosecutorial model to achieve compliance. We just do not think it is effective in the kind of academic environment that we are talking about here.

Will that from time-to-time put people in dilemmas about, you know, what to do in a particular set of circumstances and who to ask and how to get advice? You know, it is just a part of daily living and operating in an area that is regulated. You make your best

judgment about whether you need to seek advice from the agency or some other source and you try to do that.

And I think that, you know, there are all kinds of ways of getting advice, you know, on a no name basis, all that kind of thing, an answer to your question without necessarily identifying who you are. And I think that -- and I think that OPRR should be open to those kinds of tools. I mean, that is what I do a lot of the time as a lawyer for my clients is to try to get answers from regulatory agencies without telling them who my client is.

And it can be very helpful. Sometimes you can find out that you have no problem. Other times, you know, you have to give your client the bad news that, yes, they do need to report themselves or need to take some action in order to address the situation. But I think that we envision a very interactive kind of process where the answers, you know, the particular course of action will not always be clear.

DR. SHAPIRO: We have -- I have four commissioners who want to speak and we are certainly running as close to our time so I would ask the commissioners and others to be as brief as possible as we can give everyone a chance to get at least their question out.

Rhetaugh, you are next.

DR. DUMAS: I will do my best.

DR. SHAPIRO: Okay.

DR. DUMAS: What can you tell me to address my concern that in this new structure -- this new position that OPRR will not be faced by essentially the same kind of constraints and conflicts that prompted the formation of this committee for this review.

You mentioned conflicts of interest because they were a part of an agency that they were being asked to regulate so to speak. But in the Office of the Secretary, the agency just becomes bigger. It becomes a department rather than the agency so they are part of a department and they are going to be expected to regulate the activities in that department.

So I am worried about that and I am also concerned about the respect and the authority that you referred to as being necessary in order for them to do their work. Now how will they have in this position the respect and authority that they need to cross departmental boundaries?

DR. LANDERS: I will answer the second part of the question first. I think that my role in the commission was as the former government employee on the commission and I think that by being able to say that

they are a part of the Office of the Secretary and speak for the Department of Health and Human Services as a whole as opposed to just speaking for the NIH, which may have a disagreement with the CDC or the FDA, that that will put OPRR in a much more effective position in dealing with other agencies in the government, that it will be HHS speaking to the Defense Department, speaking to Agriculture, or what have you, and not OPRR three levels down in NIH trying to regulate all these organizations that have a higher stature in the government than it has.

With regard to --

DR. DUMAS: But the Defense Department will not -- this is devil's advocate.

DR. LANDERS: Yes. No, I understand.

DR. DUMAS: The Defense Department does not have to listen to the Department of HHS.

DR. LANDERS: And HHS does not have to listen to the Defense Department.

DR. DUMAS: Right.

DR. LANDERS: I mean, this is the -- I mean, if you look at -- another example is the whole issue over the Attorney General's ability to schedule and reschedule. That is the classic interagency donnybrook over, you know, law enforcement interests versus

scientific interests, you know, versus medical interests, all that kind of stuff, and I guess in some way it is very frustrating for people who are scientists because, you know, you do not just look at the science and make a decision but that is also the beauty of the political process that, you know, all these different issues get played out and the voices get heard.

I do not think wherever we put OPRR that issue and that concern is going to exist.

With respect to the first part of your question about sort of within the department, it is -- I think the conflicts will be perceived as less simply because the agency that has the most to either lose or gain by OPRR's activities will not be in a supervisory role over OPRR. There will be a broader set of influences at play at the level of the department instead of at the agency and I think that is what the perception will be, too.

DR. DUMAS: Thank you.

DR. SHAPIRO: Eric?

DR. CASSELL: Just following up on that question and on your answer. Why, in view of all the things you just discussed, wouldn't it be better if the OPRR was headed by an Assistant Secretary independent of the Secretary and Assistant Secretary for Health?

DR. LANDERS: Well, one practical issue is that the position does not exist and we were asked to, you know, kind of respect the confines of --

DR. CASSELL: An independent agency does not exist either. So if you recommended that it would have been a new independent agency so the fact that it does not exist is really -- you know, that does not seem to be a very good argument.

DR. LANDERS: Right. And I guess, you know, part of our motivation was a practical motivation. What we thought could happen. And this recommendation seems very practical. We -- I should tell you a little bit about the process, which I neglected to say at the end of my talk.

We presented our report to the Director's Advisory Committee meeting on June 3rd and immediately after the meeting Dr. Varmus sent a decision memo to the Secretary recommending that she adopt all of our recommendations. And, you know, we are told that, you know, she is actively considering them and she will act soon. I think it is possible that you -- I have no idea what is going on there. I will say that.

But I think our report gives her some flexibility to do some things that will achieve the purposes that we identified as being the important

purposes and, you know, it depends on how -- I think for immediate results moving it to the Office of the Secretary under the Assistant Secretary of Health could be done pretty quickly without her having to go the Congress to seek a legislative change.

DR. CASSELL: the trouble with immediate results, as one of our senators once told me, is that we never change anything.

DR. DUMAS: Well, you do but you do it incrementally.

DR. SHAPIRO: Larry?

DR. CASSELL: Very slowly.

DR. MIIKE: You are cutting into my time, Eric.

I have a comment and a question. I find your choice of Surgeon General very curious because except for Everett Koop, who made the office influential by the force of his personality, the Surgeon General has absolutely no influence whatsoever.

I think that what you have offered is a package but I predict that it is going to be treated as a menu, which is that, okay, which ones of these things can we do and you have already answered the question. The easiest one to do is to move the office.

Whereas, I think if you had to do one thing,

you have to give that place more resources. It is one thing to move the office and talk about conflicts and people's perceptions, et cetera, but if it does not have the resources to do its work, that is the main issue. And I think an easy thing to do is to move it without addressing the issue of resources.

DR. DUBLER: In the best of all possible worlds it would move to exactly the right place and it would be given all of the resources it needed to exercise moral and regulatory leadership in the nation. That probably will not happen. It is usually not the best of all possible worlds.

On the other hand, we did think that moving it out of its present structure was extremely important. Our choices were not great as to where it should go. Once it is moved we tried to highlight the fact that it might be more political vulnerable and, therefore, attention would have to be paid to the notion of the adequacy of its resources.

We put together, we hope, a packet of recommendations that, in fact, will support and enhance the ability of OPRR to identify developing problems in research, to respond to collect information from an advisory committee which could provide it guidance, and to offer its suggestions to the research community in

ways that will be supportive and helpful in protecting human subjects and in opening them to the benefits of research. I do not disagree. People may pick and choose and any report can be gobbled up and spit out in more or less effective ways.

DR. MIIKE: Have you been asked which of these recommendations would you really, really think are really essential or have you just been -- offered to give them as a package?

DR. LANDERS: We have not been asked that question.

DR. DUBLER: I think we would be hard put without going back to the panel since we think the recommendations really are complimentary and necessary as a packet.

DR. LANDERS: On this question of resources, again I will go back to my experience teaching administrative law, there is a school of thought that, you know, there are statutes and there are regulatory roles that agencies in theory ought to be fulfilling. But really the Congress gives them exactly as much money as the Congress thinks that they need to do he job that Congress identified.

Now we may disagree about that judgment but there -- you know, there is -- I think the best that we

can do is to try to have a structure in which the decisions at least are transparent to the public about the resource questions and the policy making questions, and that is what we have tried to do.

DR. SHAPIRO: Please go ahead.

DR. DUBLER: I just do not want to end by -- you might be ending the discussion and I just wanted to point out that Dr. Terry Wettle (?) who was sitting there with our overheads but really has been just a critical person in this process as Deputy Director of the National Institute on Aging. She really was someone who provided us guidance and direction and support, and we would like to thank her very much.

DR. SHAPIRO: Thank you. Thank you for being here this morning.

The session is not quite over. I have one small parochial question and then I will turn back in case Alex still wants to ask his fourth question. I will give him an opportunity to do so.

And it really is motivated by your last comment regarding openness. I have what I think is this general notion that in the compliance area, that particular area, that the notion of audit, either internal or external audit, is a very useful tool and yet it is not widely used at all. In fact, it is not used

for the most part.

It is my own view that an appropriate system of that kind might, in fact, substitute for a lot of very complex regulations and resources that are never there and so on and so forth. I am just asking a question of whether that issue ever came up as you went through these various possibilities.

DR. LANDERS: Only to the extent that we thought that institutions ought to know more about what was going on in their institutions in this very important area and I think that your comment speaks to that notion.

DR. SHAPIRO: Alta?

PROF. CHARO: Is there time for one more?

DR. SHAPIRO: Yes.

PROF. CHARO: I apologize but one of the issues that has been circling around in the more general discussions about human subjects protection is the need or the absence of a need for some kind of central office that either serves to harmonize various federal departmental choices about what kinds of protections to adopt and how to interpret the language that they have adopted and/or to handle specified subtopics such as research with the mentally infirmed, the RAC with gene therapy, now possibilities in the area of stem cells, or even there has been some discussion last week at Fogarty

about certain kinds of international research.

I would be interested in knowing how, if at all, that was part of your discussions as a factor that might become yet another kind of leg on this stool in the federal system.

DR. DUBLER: It was very much a part of our discussion. This panel with its quite narrow charge looked at the maximization of optimal functioning given the structure that we now have. OPRR has responsibility for the Common Rule and, therefore, the two areas that you just suggested could appropriately be discussed within the Common Rule. There has been no forum established in which different departments could come together to air the sorts of research they are thinking about, to think through the human protection problems that are presented, and to see whether cross-departmental solutions are really possible.

We would hope that OPRR would play that role. It may not be possible at the edges of research but there is certainly greater latitude for OPRR to exert moral leadership, regulatory leadership, and educational leadership than it now uses as the basis for interpreting its role and its behavior. So we would hope, in fact, that an OPRR, which was relocated higher within the department, was able to reach out to other departments,

and able, in fact, to become that center for the discussion of developing interesting, complex dilemmas in research, in fact, that it could play that role.

DR. SHAPIRO: Thank you. Any further questions from members of the commission?

Once again let me thank you both very much for agreeing to spend the time to come here today. We appreciate your work and the work of the panel.

The formal meeting of this commission is adjourned.

(Whereupon, the proceedings were adjourned at 12:10 p.m.)

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