38th MEETING

NATIONAL BIOETHICS ADVISORY COMMISSION

Hilton Washington Dulles Airport
13869 Park Center Rd
Herndon, VA

March 1, 2000

Eberlin Reporting Service
14208 Piccadilly Road
Silver Spring, Maryland   20906
(301) 460-8369

I N D E X

Opening Remarks

Harold T. Shapiro, Ph.D. 1

ETHICAL AND POLICY ISSUES IN THE OVERSIGHT OF HUMAN SUBJECTS RESEARCH

Overview of Work to Date

Marjorie A. Speers, Ph.D. 3

Panel I: Oversight of Human Gene Therapy Research

Claudia Mickelson, Ph.D., Chair Recombination DNA Advisory Committee 9

Lana Skirboll, Ph.D., Director, Office of Science Policy, National Institutes of Health 34

Kathryn C. Zoon, Ph.D., Director, Center for Biologics Evaluation and Research, Food and Drug Administration 42

Discussion with Commissioners 55

Panel II: Implementation of the Common Rule -- The Case of Revising the Expedited Review Categories and the Case of the Classified Research Rule

Michele Russell-Einhorn, J.D., Director for Regulatory Affairs, Office for Protection from Research Risks 93

Discussion with Commissioners 104

I N D E X (Continued)

Panel III: Alternative Federal Regulatory Systems

Diane Flack, M.S., Senior Health Physicist, Rulemaking and Guidance Branch, Office of Nuclear Material Safety and Safeguards, Nuclear Regulatory Commission 119

Jane Ley, J.D., Deputy Director for Government Relations and Special Projects, Office of Government Ethics 130

Discussion with Commissioners 141

Panel IV: Definition of Research

Andrew Nelson, Executive Director, Health Partners and President HMO Research Network 158

Mary Durham, Ph.D., Vice President for Research, Kaiser Foundation Hospitals 161

Discussion with Commissioners 182

Panel V: Update on Congressional Initiatives

Paul T. Kim, J.D., M.M.P., Counsel, Congressman Henry A. Waxman, United States House of Representatives 212

Souheila Al-Jadda, Legislative Aide, Congressman Dennis J. Kucinich, United States House of Representatives 225

Discussion with Commissioners 231

PROCEEDINGS

OPENING REMARKS

HAROLD T. SHAPIRO, Ph.D.

DR. SHAPIRO: All right. Colleagues, we have a very full day so I would like to call our meeting to order. I am expecting a few more Commissioners shortly.

We have a rather full agenda, as I have just said, which will take us roughly until 3:00 o'clock this afternoon.

We have a number of panels we are going to hear from today and they are all outlined in your agenda. The first one will begin in a few moments dealing with the oversight of human gene therapy research but I want to remind the Commission that our particular project now is the oversight of human subjects research and it is in that context that we are going to be listening to various panels today.

The human gene therapy research is simply the first panel.

We have an example regarding classified research and dealing with that in the second panel and so on.

Alternative federal regulatory systems will be the third panel.

Our project is a broad overview of the human subject research system in this country to try and see what we can learn from the experiences over the last decades and see if we have any useful recommendations to make going forward.

I am going to turn to Marjorie in just a moment who will give you an outline of how that project is going and what the time schedule is. We are, roughly speaking, aiming for a report near the end of the year, beginning of the next year, in that period.

There is an awful lot of work underway. We have a considerable amount of staff who will be working on this from now until then and I will let Marjorie fill you in on details.

So why don't I turn to Marjorie right now and then I would like to say a few words before we begin with the panel, which -- thank you very much for being here.

It will only be a few minutes until we get to you so thank you very much for your patience.

Marjorie?

ETHICAL AND POLICY ISSUES IN THE OVERSIGHT OF HUMAN SUBJECTS RESEARCH

OVERVIEW OF WORK TO DATE

MARJORIE A. SPEERS, Ph.D.

DR. SPEERS: Thank you.

As Harold said, the Oversight Project is progressing as planned.

I want to introduce to my left, Alice Page, who all of you know. She is going to be the project manager for the Oversight Project and will be transitioning to the Oversight Project when the International Project is finished. As she has time to spend on this project now, she will be doing so and so I have asked her to sit at the table with us today.

In your briefing book there is a copy of the outline for the report as I promised I would have available for you at this meeting. If we have time at the end of the day, which we have scheduled some time under "Next Steps," we can discuss the outline for the report if you wish. I do not want to do it this morning because of our tight schedule.

I am pleased to report to you that we have confirmed now 11 authors for the proposed Commission papers. We are talking to one other author, potential author, at this time but I expect that we will have that person confirmed and, therefore, all 12 papers that we proposed I would like to say are really underway.

A list of the paper and authors will be shared with you in the next week or so. We have asked the authors to complete their papers by the end of May or by early June. And as such then you have a substantial amount of text to read, background text to read for this project in June and July.

We will schedule those authors to present at Commission meetings accordingly. Meaning that they will either present in the June, July or September meetings.

In addition, we expect to have a substantial amount of the text that staff will be preparing, particularly with initial recommendations on the topics that we are dealing with today, by June and I expect that we will spend a substantial amount of the summer when the Commission is not meeting in August preparing text for you so that by the fall -- by the September/October meetings you will be reviewing chapters and recommendations for this project because, as Harold said, we anticipate having it completed by the end of the year or early next year.

Today we will continue with the two topics that you have been discussing. One is the adequacy of the current regulatory framework and structure and the second is on the definition of research.

As you listen to the first three panels keep in mind that you will be making recommendations about the current regulatory system, perhaps proposing an alternative framework and structure, and perhaps recommending oversight mechanisms that are other regulatory.

So, as I say, when you listen to the presentations today listen to them with the sense that at probably the May meeting or the June meeting we will be coming back and specifically looking at potential recommendations.

At the April meeting we plan to have representatives from the private sector speak about conducting human research and IRB review.

And at the May meeting we plan to present two models of protection from other countries. These are models that are comprehensive in that they apply to all research, all types of research, and are implemented without a regulatory framework.

Once we have completed those discussions then I think it will be time for the Commissioners to consider recommendations for the structure in the United States.

The fourth panel addresses issues related to the definition of research. Today specifically in the area of health services. At the January meeting you heard about problems of applying the definition of research to public health and today you will hear about the gray areas in the definition related to health services research.

In April we will devote a substantial amount of time to hearing about applying the definition of research and the regulations to the social sciences and to the humanities. It is anticipated that at the April meeting there will be time for substantial discussion on this topic and for considering recommendations.

We will in the next couple of weeks get some text to you to consider before the meeting relating to how this Commission might want to make recommendations regarding activities that ought to be regulated for protection.

I think, Harold, that is really all that I would like to say so we can move along.

DR. SHAPIRO: Thank you very much. Let's turn directly then to our first panel. If any of you have any questions for Marjorie on the general outline and so on, we can pick that up later on today as we have time. I want to turn now to our panels.

I want to really do just two things to

introduce the panel. One, I want to thank the panel members for coming. We very much appreciate your presence here today and we know you have taken time from busy schedules to share your thoughts with us on this issue and we are very, very appreciative of you being here.

Second of all, I want to remind both us and anyone else who might be listening that, of course, while we want to look at human gene therapy research as an example or seeing what it is that we can learn regarding the overall system of human subject protection in this country, it is not our focus or our mandate to investigate any particular cases. We are not investigating cases. That is not part of NBAC's mandate.

What we are trying to do is simply learn from experiences that we have had with the existing system.

And since this is something which has obviously been very much of interest of late and there has been a lot of ink put to a lot of paper on this issue in recent weeks it should not distort our view of this, which is just simply trying to see what we can learn from this and what we -- the people who know a lot about the details can really tell us about it.

So that will be our focus as we go through not only this panel but other panels that deal with human subjects protection in particular areas.

Now we are going to -- I understand that somehow the panelists themselves got together and decided on a slightly different order than is on your agenda. Dr. Mickelson is going to be first followed by Dr. Skirboll and Dr. Zoon so they will go in that order.

So let me now turn to Claudia -- Dr. Claudia Mickelson from MIT.

Thank you very much for being here today.

PANEL I: OVERSIGHT OF HUMAN GENE THERAPY RESEARCH

CLAUDIA MICKELSON, Ph.D., CHAIR, RECOMBINATION DNA ADVISORY COMMITTEE

DR. MICKELSON: I would like to present some overheads. Will that be possible?

DR. SHAPIRO: Certainly.

DR. MICKELSON: You have handouts but I would like -- I have them ready up here.

DR. SHAPIRO: Okay.

DR. MICKELSON: And I will stay to time.

DR. SHAPIRO: We will do the overheads. We will put them on there.

DR. MICKELSON: Okay. Well, they are right here.

(Slide.)

Well, I would like to thank the Commissioners. You all have copies of the overheads that I will be presenting and I would like to thank you for the opportunity to begin discussions with this group and I am sure that this will probably be the first in a number of discussions on the oversight of gene transfer research.

I am going to give you some idea of the past history of the NIH oversight role, how it functions today, and then what some of the issues are that we face and the steps that various parts of NIH and the oversight process within NIH have taken to change these.

(Slide.)

I am going to outline the U.S. Framework for oversight in human gene research, gene transfer research, and just as a brief explanation of what gene transfer research is:

Within the context of overall drug research within the United States, gene transfer research is a very small portion of that and it deals with development of methodologies with which to introduce genes into humans to either replace or add functions

to cells in which there are defective genes or nonfunctional proteins.

There is also -- the second major group is the introduction of genes into humans to modify cellular function, either to enhance the immune system or to turn on the immune system say in the case of cancer therapies.

As well, there are also a number of trials and we will look at what percentage those are, which are, in fact, basic science. In other words, trying to understand the basic science of how -- where cells go, how tumors re-arise and/or metastasize in humans.

(Slide.)

The levels of oversight for human gene transfer research are both at the federal and the local level. NIH oversight is embodied by three -- in three arms. The NIH Guidelines, the Recombinant DNA Advisory Committee, and then at the local level Institutional Biosafety Committees, which are governed by the NIH Guidelines.

The FDA is the second arm at the federal level with their laws, regulations and guidances.

The third is the Office of Protection of Research Risks, which also oversees besides human subject research the use and protection of animals in

research.

At the local institutional level all of the responsibilities of institutions for protection of human subjects in human gene therapy is also outlined. OPRR looks at the structure of the Institutional Review Boards. The NIH Guidelines look at the structure and responsibilities of Institutional Biosafety Committees. And the investigators fall -- and have responsibilities for all three groups.

(Slide.)

If you look at a comparison of the local oversight -- of the oversight roles at the local level you will see that -- and it is harder to see than I had hoped -- that at the local level there are two main committees that actually end up being involved in oversight of human subjects within human gene transfer experiments, which is the box at the very far right end as we look at that.

Basically the two groups up there, the Institutional Biosafety Committee and the Institutional Review Board.

And the Institutional Biosafety Committee has responsibility for all of the intermediate steps leading up to the human gene transfer, the development of a human gene transfer clinical trial because that role is outlined in the NIH Guidelines.

Whereas, Institutional Review Boards come in at a later level with the beginning of the development of use of animals, development of animal models and preclinical studies as one part of their role and then also the Institutional Review Boards come into play at the very far end with the actual institution of a trial.

The NIH Recombinant DNA Advisory Committee only comes into play, as does the FDA, once a clinical trial protocol has been written and submitted to either agency.

However, the NIH Guidelines have oversight responsibilities through the local institutions throughout the whole process of development of therapeutic vectors, development and design of clinical trials, as well as development of animal models.

(Slide.)

The NIH oversight mechanism has three arms. The guidelines, as I have spoken of, the Office of Biotechnology Activities, and then the Recombinant DNA Advisory Committee.

(Slide.)

The NIH Guidelines -- I am going to go

through each three of those very quickly.

The <u>NIH Guidelines</u> apply to all projects, whether they are funded by NIH or not, that involve recombinant DNA technology and is conducted at or sponsored by institutions that receive NIH support for any projects involving such techniques.

Institutions and investigators, therefore, that receive NIH monies must comply with the <u>NIH Guidelines</u>. That is stated directly within the <u>NIH Guidelines</u>. And that impinges on then privately funded research or industry sponsored research that has been conducted at an NIH institution.

The institution then has an obligation to ensure compliance with the <u>NIH Guidelines</u> and that means all submitting and reporting responsibilities that are outlined in the guidelines. It then becomes the institution's responsibility to ensure that the trial is conducted in accordance with the <u>NIH Guidelines</u>.

(Slide.)

The role of the NIH Recombinant DNA Advisory Committee is the protection of patients, the public, the community and the environment. That is throughout all of the responsibilities of the Institutional Biosafety Committee. The committee is also involved in policy development which is then expressed in changes to the Recombinant DNA guidelines.

Part of our responsibility is also to look at the scientific quality of the protocols that come to the committee. We do that by assessment and review of individual protocols looking for generic issues that need public discussion and can result in the improvement of the scientific quality of the protocols so that the information that is gained is worthy of the involvement and engagement of patients.

We also try to ensure public access to all information obtained from gene therapy trials as well as their initiation and the inclusion of clinical endpoints and then the target population.

Probably one of our biggest efforts will be in the future education in both the public and the industry as well as patient populations as to the status of the field, the role of the RAC and how the three groups can interact with the NIH Recombinant DNA Advisory Committee in a more productive manner.

(Slide.)

The Office of Biotechnology Activity coordinates the activities of the committee, coordinates our oversight activities and policy development. They also are responsible for protocol management, development and maintenance of a database, as well as establishing and running and organizing for the committee Gene Therapy Policy Conferences, as well as they are the actual execution arm for our education and public and industry interface.

(Slide.)

I would just like to give you a brief background on the status of human gene therapy trials.

This first overhead -- go on to the next one.

(Slide.)

I am speaking a little quickly to stay within 15 minutes or so. I apologize.

This particular graph shows the dramatic increase in the number of clinical protocols submitted to the NIH office by year. And as you can see, since the actual first approval and review of a clinical trial in 1988, by February of this year we are up to about 390 clinical trials that have been submitted to the NIH of Biotechnology Activities. That does not mean that there are 390 active clinical trials. Some of the earlier ones have not proceeded and have stopped but that is the total number registered with the office.

It looks like the year 2000 will be even more with 91 protocols submitted this year.

(Slide.)

The next overhead shows the gene therapy trials by clinical indication and as you can see the greatest number of clinical protocols that we see are aimed at development of new cancer therapies, a smaller percentage -- a much smaller percentage, 13 percent, are aimed at the treatment of monogenic diseases.

Monogenic diseases are those disorders which are characterized by a defect in a single gene, not multi-component disorders but single gene defects.

As well as the other -- in decreasing order then cardiovascular research, use of gene therapy to improve or engender revascularization of areas.

(Slide.)

The next overhead shows gene therapy trials by phase. The predominant number of gene -- oops. I am sorry. That is fine. My mistake.

Delivery -- the largest -- most of the research involves use of some type of defective virus to deliver genes to the humans, whether it is injected directly into the patient or whether cells are removed from the patient and then the cells are infected and then reintroduced into the patient. That is the *ex vivo* treatment where cells are removed and then transduced with a viral vector. It is the route of administration for most of the trials that use retrovirus.

Adenovirus, which is one-quarter of the clinical trials use adenovirus as its delivery system. Adenovirus tends to be used more *in vivo*. It is given directly to the patient usually by direct injection into tumor.

The other words that you see up there, most of them are different types of viruses, vaccinia and fowl pox. Those are different types of viruses that tend to be more immunogenic. And herpes simplex virus.

And a growing -- while this is a reflection of where the field stands now, there are a number of new vectors in development. One having already reached use in humans, which is the AAV, which is a very small adeno-associated virus. And that, while it is only two percent now, is something that we expect to see in much larger numbers in the future.

Again we would expect to see some of the newer -- you can tell from the literature which vectors are in the pipeline and will be coming forward to clinical trials and those -- once safety issues are resolved -- would probably -- we would probably see things like lentiviral vectors and/or attempts to correct defects *in situ* with repair.

(Slide.)

The next overhead shows gene therapy trials by phase and it gives an indication of the status of the field. Phase I is the earliest and the very first step in development of any type of therapeutic drug and Phase I studies are only aimed at ensuring safety.

The types of information that you gather in a Phase I trial tends to be what level or dose can be given to a patient before you reach a maximum tolerated dose before you begin to see adverse events within -- or serious reactions within the patient.

And then the next lowest level is what is considered the maximum tolerated dose for use in that patient.

As you can see, most of the trials are that -- of the 390 that we have looked at are -- almost 87 percent are in Phase I. There is a small number, 12 percent, in Phase II. And there is only one percent or three of them that are actually at Phase III trials. Those Phase III trials are trials involved in cancer therapy.

(Slide.)

The next overhead shows some of the scientific issues that we have encountered in assessment and review of gene transfer research.

One of the issues that is somewhat different about gene transfer research is not just that we are attempting -- that the protocols are aimed at attempting to modify the human genome but that given the target populations there is a compression generally of the phases of the trials in that the patient populations that can be enrolled in some of these studies, in particular for monogenic diseases, is very small.

So that there are attempts at measurements of efficacy in the Phase I trials mainly because of the small number of patients so that in order to make the enrollment of the patients worthwhile and to get as much scientific value out of the clinical trial there is -- some of these Phase I's are, in fact, Phase I/Phase II so that we always ask for some measure of the actual biological activity of what is going on if possible.

Scientific issues that the committee looks at and has faced are -- and discusses quite extensively is the -- are the issues of vector safety. Is the delivery method -- what are the implications?

What can happen *in vivo* or *ex vivo*? Will a replication defective vector remain defective? Are there issues of recombination and stability, homogeneity of the vector preparation?

A very large issue is the specificity or the lack of specificity of the vectors used today. There are no vectors that will hit only particular cell types. Even human pathogens have very broad ranges within the human body. And tissue specificity.

So that for -- in general, the cell and tissue specificity is lacking and that is, in fact -- one dilutes the clinical -- any therapeutic efficacy of the vector but it then does represent safety issues.

It also leads to issues of potential for inadvertent germ line gene transfer which we will look at a little later.

It also looks to the possibility if it is used *in utero* if you have nonspecific tissue and cell specificity that it may lead to inadvertent germ line gene transfer in -- if *in utero* protocols go forward.

The other issues are -- these are fairly standard and we see them repeatedly but issues of persistent and regulated transgene expression and then the potential -- we look at secondary effects of insertion of any DNA into the genome can have effects on neighboring genes.

Shedding and exposure of these vectors to nonpatients and/or families.

And then just the long-term effects of gene transfer.

The ethical and public issues that we discuss -- the next overhead. Thank you.

(Slide.)

-- that are always dealt with in the protocol reviews, we attempt -- hope to and try to pay attention to patient safety. The informed consent documents receive a lot of attention.

We attempt to look at what is an acceptable level of risk for that potential patient population and whether we feel the informed consent document is actually an appropriate method of communication of this risk.

We have looked at and dealt with *in utero* gene transfer protocol, a potential protocol.

And the RAC has reached statements on *in utero* gene transfer and also maintains its statement on germ line gene transfer.

And the issue of *in utero* gene transfer, the RAC policy is that any attempt to do *in utero* gene transfer at the moment is premature. We do not know -- there is not enough basic science known about development in embryos nor is there enough control within the vectors but that it was not a ban. The words were used that it was "premature."

All of these policy statements are available on the web as well.

There has been no attempt to change the RAC's statement on germ line gene transfer. Again the RAC will not entertain any protocol that is specifically aimed at changing germ line gene transfer.

The issue of inadvertent germ line gene transfer where there is a very -- there has been no documented proof that that has occurred, in cooperation with the FDA we have asked and it has happened that there be mention of the potential for risk of inadvertent germ line gene transfer in the informed consent documents.

Enhancement is another issue that is brought up during discussion in the committee and as you will see later we have had a policy conference to attempt to deal with that and basically where we stand now is that we have no agreed upon definition of enhancement and there is a very large gray area.

The way I approach it is that there -- we can reach agreement on what types of therapies and uses are not enhancement which could be the least upper bound of the problem. There are areas that we could agree upon that are -- would be enhancement and that could be the greatest upper bound.

And then we should have discussions in an attempt to reach some discussion on the gray area in between and try to bring at least upper bound -- the greatest upper bound and the lowest upper bound together to reach a median.

If we could go on then to skip the next one and on to the NIH oversight of gene transfer research. I will rush through the origin and evolution.

DR. SHAPIRO: May I interrupt?

DR. MICKELSON: Yes.

DR. SHAPIRO: I very much apologize for interrupting --

DR. MICKELSON: That is all right.

DR. SHAPIRO: -- what is a very interesting presentation. I am conscious of time.

DR. MICKELSON: Oh. Am I already -- okay.

DR. SHAPIRO: And the part that really is of greatest interest to us -- if you do not mind me making a suggestion --

DR. MICKELSON: Surely.

DR. SHAPIRO: -- is what the RAC is doing today.

DR. MICKELSON: Great. Let's go to that which is -- and maybe if -- since you already have your things in hand, we probably do not -- well, for the audience.

The current protocol review process, which is probably --

DR. SHAPIRO: It is on page 7 in the handout for the Commissioners that have it.

DR. MICKELSON: Yes. It is after the overhead that says "Today."

The current protocol review process. The protocol review process has gone through a number of changes. At the moment the protocol review process is outlined in the following three to four overheads.

Clinical trial protocols are registered with ORDA. It is now called the Office of Biotechnology Activities. They are registered with the office after local institutional review board and IBC review and once the local committee review and approval has occurred they are submitted to the -- to the Office of Biotechnology Activities where the office prepares a summary and forwards the protocol and summary to the committee.

Within -- after two working days after submission the RAC -- the committee members then determine if the protocol is novel and whether it warrants in depth review and public discussion.

The investigator is notified of the RAC decision within 15 days and non-novel protocols are exempted from any further review by the committee.

Novel protocols or protocols that three members of the committee have decided need some type of in depth review and/or public discussion are discussed by the entire committee at its quarterly public meetings.

(Slide.)

The RAC makes recommendations, submits written reviews to the investigator. There is a question and answer period before the committee meeting but after the public discussion of the committee the recommendations are written and then forwarded to the investigator, to the local institutional review board, IBC, and the FDA as well.

(Slide.)

Then the RAC minutes of the discussion of the protocol are posted on the web.

Each investigator receives a letter that gives the outline of the RAC review and the public discussion and reiterates the necessity to comply with the guidelines and the reporting of adverse events.

(Slide.)

I think that one of the issues that has been raised in the review of the NIH -- by the NIH Recombinant DNA Advisory Committee about review is the -- and there was a table that you do have in your overhead -- is that the change in the ability of the committee to approve or disapprove protocols, and the next overheads deal with that.

(Slide.)

Points that need to be considered about the approval of protocols: It should be understood that approval is the decision of the NIH Director taking into account the recommendations of the NIH Recombinant DNA Advisory Committee. The NIH Director decided to give up approval of NIH -- of protocols submitted to the NIH Office of Recombinant DNA Activities.

What was not understood at the time was that although the NIH Director gave up approval that did not relieve any investigator's responsibility to comply with the NIH Guidelines, which encompassed both registration and the necessity to submit protocols to the NIH Office of Recombinant DNA Activities.

(Slide.)

In order to try to address this issue of lack of approval and to enhance the NIH/RAC review process, the NIH committee proposed a change to the <u>NIH Guidelines</u> that had to deal with the timing of submissions so that the NIH committee could review protocols before the local committees had completed their review process so that the NIH committee would review protocols that had at the same time that they were being submitted and reviewed by the local institutions. This would be before the FDA process of review or initiation -- the IND could go forward because institutional review board approval would not have occurred so that the RAC review would occur before patients could be enrolled and the trial started.

The rationale for this change -- proposed change in timing action was to allow RAC input into the design of preclinical studies, input on the informed consent, and early identification of issues associated with this particular protocol.

(Slide.)

It would avoid multiple layers of a synchronous review and it would ensure that patients that were not consented -- that patients could not be consented and enrolled in a novel research protocol prior to the public discussion and the RAC review.

The committee had voted in favor of the proposal of this change in timing and the FDA issued letters to sponsors recommending that RAC review occur prior to protocol initiation.

(Slide.)

The NIH Director's final decision on this particular timing action is awaiting input from the Advisory Committee to the Director's Working Group.

(Slide.)

The Office of Biotechnology Activities and the committee are making increased community and outreach efforts both within NIH, liaisons with other institutes, as well as academia investigators, as well as with various professional societies.

We are also hoping to encourage and actively generate a better communication with industry representatives as well as the patient community.

(Slide.)

Before we had become engaged in this quite detailed review of the NIH oversight process the committee had pulled together a plan for systematic analysis and revision of the NIH Guidelines attempting to look at their clarity and their currency.

We have various working groups put together to look at the scope of the NIH Guidelines to try to increase them to focus on the aim of the research and not a specific technology and that is to try to attempt to be able to capture and address the issues that would be raised by new technologies that are on the horizon that are aimed at genome modification.

We have attempted to -- and have a working group in place to look at the vector biosafety and containment issues.

These plans and initiatives will go forward as the committee resolves some of the issues that are facing it today and these will be part of our plan of action for the next year.

Also -- and I do not know if Dr. Skirboll will address the other Office of Biotechnology and Committee initiatives --

(Slide.)

-- and these are aimed at establishment and enhancement of the clinical data base as well as the establishment of a clinical data management subcommittee.

Also, we will attempt to enhance and further use web accessible submissions and a web -- and create the web accessible database so that not just the public is aware of what is the status of current trials but that patients can also access information on the status of trials.

(Slide.)

This is also -- the public access to this information is also a foundation of increased scientific quality in the protocols.

And with that I would like to hand over to Dr. Skirboll. I apologize for going too long.

DR. SHAPIRO: Thank you very much and thank you for the many -- the material you presented, including the material we did not get a chance to review today but we have copies of it and we are very grateful. It is very helpful to us.

DR. MICKELSON: Any questions?

DR. SHAPIRO: We will try -- if you do not mind we will try to take questions after we have heard from everybody and we will take --

DR. MICKELSON: Sure.

DR. SHAPIRO: -- all our questions at that time.

So let me now turn to Lana Skirboll. As you all know, Dr. Skirboll is Director of the Office of Science Policy at NIH.

Thank you very much for coming.

Let's see if that is working. If not, you can --

LANA SKIRBOLL, Ph.D., DIRECTOR

OFFICE OF SCIENCE POLICY,

NATIONAL INSTITUTES OF HEALTH

DR. SKIRBOLL: Is it on?

DR. SHAPIRO: It is on.

DR. SKIRBOLL: I think it is on.

I will try to do two things. I will try to be short and talk fast so we can move forward here. I am short and I usually do talk fast so that is good.

What Claudia described is -- put in perspective, is quite unique for clinical research. It is the one area of clinical research in America in which there is this extra oversight body, the RAC.

And NIH's oversight is, as Claudia pointed out, comprised of three entities, the guidelines, the RAC and the Office of Biotechnology Activities. They each offer unique but important components of NIH's oversight role in gene therapy.

I am always happy to be here with my colleagues from the FDA and talking about gene therapy because we offer both, I think, important different and complementary roles in the oversight of this.

There are many things that NIH has been doing well in this arena. I know recent news reports have suggested that this -- there is considerable problem with this oversight but let me just recall briefly to you that our mandate is public discussion.

This is the thing that we offer uniquely to this area of clinical research and we have been doing that. We still review novel protocols in a public forum. We offer advice to the entities that Dr. Mickelson referred to. We have policy conferences. We have changes to the guidelines that are discussed in a public forum, public disclosure of data, protocols, adverse events and public discussion and education.

Turning to recent events, the very tragic death of Jesse Gelsinger, I think for all of us and for NIH in particular is an example of a model of what NIH uniquely does offer to this arena.

Upon notification of the death of Jesse Gelsinger by Dr. Wilson, NIH immediately went into action. We notified every investigator in the field. We formed a RAC adenoviral working group.

And we, most importantly, held a public meeting. One that I think you all read about in one form or another in which scientists, the public and the press could all come together, hear about this research, hear what the facts were with regard -- both with regard to the death of Jesse and in particular the safety of adenoviral vectors. Again an important service, I think, to both the research community and the public.

What did emerge from that quick and rapid response of the research community to the event happening at U. Penn was that it revealed that we were not getting sufficient reporting of adverse events.

Before I go into that and NIH -- how NIH is dealing with that issue because I think it is an important one when you look at the oversight of human subjects research, I want to go back. Allow me for just a few minutes to talk about what is an adverse event and what it may mean and what NIH's role in it is.

I do not have to tell you all that clinical research is an experiment. If we knew the outcome we would not have to do the experiment in the first place. The reason that we have the human subjects oversight system that we do have is that research itself is risky. It -- adverse events, I think, have been taken out of context in recent.

We need to make sure that when patients are in research, of course, that we minimize risk to those subjects and we do that through a variety of ways, both the system and most importantly through what we are calling informed consent.

I actually do not like that word "informed consent." It presupposes consent. I prefer "informed decision making." We do not assume that patients are going to consent in a trial and that was one of the issues that certainly emerged in the testimony of Paul Gelsinger.

In the best of circumstances, in the best of trials there are adverse events. What is an adverse event? Well, it is a life threatening event, death, inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability.

It can be related to the therapeutic intervention. It can be unrelated. It can be related to another part of the trial. Some intervention part of the trial that is not necessarily in the case of gene therapy. It could be related to surgery or another chemotherapeutic agent.

It can be expected. It can be unexpected. It can be expected because we know -- what we know of previous human intervention or from animal studies.

It can be related to the treatment but it can also be due to underlying disease. And, as you know, and I hope we have made it clear that with regard to adverse events in gene therapy many of the patients here are quite sick. They are at endstage disease.

And the many adverse events that I think emerged in the public, the hundreds and thousands that emerged as we started to tell this story were misinterpreted as related to the treatment. They were, in fact, in large part due to underlying disease.

In fact, to date, in looking through these adverse events, and I think Dr. Zoon can certainly address that, too, 4,000 patients have been treated in gene therapy trials and we only know one patient at this point that we think died as a result of the gene therapy, directly related to the gene therapy.

But it is true that the <u>NIH Guidelines</u> require all serious adverse events be reported to the NIH. This is again very unique. It is completely unique with regard to oversight of human subjects. It is the one arena in which adverse events are made public. Every investigator gets a letter that says they must submit those adverse events.

I could go into the statistics. Dr. Patterson is here to answer those questions but I will not go into that right now. What I want -- I want --

I want to relay here, and I would welcome some discussion, is this issue of public reporting of adverse events.

We are going out now. We are working to ensure that every investigator does this. We are sending out letters and phone calls. We are sending out site visits to make sure investigators understand this and institutions understand it.

But the discussion right now is focusing at the RAC on why should NIH get adverse events and what is the timetable of it. Is this a good model for the protection of human subjects? What might the role be for adverse events?

We have seen our role really three-pronged and one that I think merits modeling. Public disclosure of adverse events not just for the public per se but for other investigators to actually see what is happening in trials so that it would inform trials, make subsequent trials or ongoing trials safer, and also for long-term trend analysis of adverse events that might not emerge if you were looking at these one trial at a time.

We are still discussing. There is a working group of the RAC discussing when the NIH should get them.

Is everything that Claudia and I have described, this oversight process, is this enough for gene therapy? That question has been asked. It is a reasonable question. Reviewing of novel protocols, this advice to the FDA, public discussion. Is this enough? Is it too much? Is it a model that is good? Is it a model that should be revamped?

The NIH Director has asked a subcommittee of the Advisory Committee of the Director to look at that and I should add that one of the things they will be looking at is return to approval.

Finally, I would like to point out that the Department of Health and Human Services has taken these events quite seriously and there is in-depth discussion in the department looking at the events that took place with the death of Jesse Gelsinger and determining whether there are other actions that the department can take to further ensure the safety of patients and I think within the next few days the department will be announcing some of these so I will take questions.

I hope I was short enough and not too fast.

DR. SHAPIRO: Thank you very much. It is extremely helpful and we will certainly come back to questions in a few moments.

Let me now turn to Dr. Zoon.

Dr. Zoon?

KATHRYN C. ZOON, Ph.D.

DIRECTOR, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION

DR. ZOON: Thank you.

I would like to, one, thank the Commission for inviting me here today to speak on the regulation of gene therapy with a particular emphasis in the FDA on our activities and I will also comment on our interactions with the NIH and the RAC.

As many of you may know, human gene therapies is one of many complex biological therapies that are regulated by the FDA and these would include such products as vaccines, live viral vaccines, bacterial vaccines, blood, blood safety, blood products, blood derivatives, allergenic products, what I would call more conventional biotech products such as recombinant DNA derived proteins and monoclonal antibodies.

So the agency has an experience in dealing with a variety of complex therapies that have in some cases proven benefit and in other cases such as gene therapy are still under investigation.

While we will spend today discussing gene therapy, really many of the issues that the agency deals with, with gene therapy, are very similar to all the other biological products that the agency regulates. Probably the major difference that I would say is our dual role with the NIH and the RAC in the oversight of gene therapy products.

As many of you know, any type of clinical research in the United States may proceed only if they have an authorized investigational new drug application, and this is also true for human gene therapy.

At this -- the regulations and the laws that govern the regulation of gene therapy are the Public Health Service Act and the Food, Drug and Cosmetic Act. We also have a series of regulations found in the Code of Federal Regulations.

And I have in some overheads, which I am not going to use in the interest of time, provided you with the vast array of regulations which apply to this therapy and some time in your spare time I am sure you will be delighted to read them.

Over the past 11 years, though, gene therapy, as has been demonstrated, has had a vast increase in activity. Back in 1989 we only had one gene therapy protocol. Now last year we received 55 gene therapy protocols. And I think this is a reflective overall of the exponential growth in this area.

And while this therapy is growing remarkably, this therapy holds a lot of promise for severe and life-threatening illness for which there are no alternatives. Yes, it has risks. This is common for clinical trials as Dr. Skirboll says. There is no entry into a clinical trial without risk. And I believe in this case, this is a balance that we at the FDA have to deal with every day, and in gene therapy holds to that context.

So how does the agency deal with the regulation of gene therapy products? Well, we do it by having state-of-the-art knowledge in the science and the technology. We have experts in molecular biology, virology, experts in pharmacology, toxicology, medical officers that have a vast array of expertise in this.

FDA has developed regulations and policies over the years that apply to gene therapy as well as specific guidances that assist in the conduct of trials in gene therapy as well as other clinical trials and how to provide guidance to individuals or sponsors that they be making and preparing gene therapy products and the types of experiments that the agency expects to see.

This is not done in the FDA alone. It is an interactive process. We go to scientific meetings. We hold scientific meetings. We have advisory committees. We participate in the RAC. We have our own FDA advisory committees to get as much technical and scientific advice to provide the foundations for our decision making at the agency.

But we also are very much aware that gene therapy requires public discussion and I think that issue and our cooperation with the RAC over the years is very evident by the fact that FDA has been a participate in this process and provides often times much information and discussion at the RAC in order to provide a public forum in which to discuss those issues.

FDA also has surveillance and compliance activities and I will go into these in a little bit more depth.

Well, to achieve our task I will just briefly talk about what we do. Much of the gene therapy that we -- that is currently ongoing is in the investigational phase. There are no licensed products for gene therapy at this time.

Most of the gene therapy procedures that are currently ongoing are in Phase I and Phase II so this

means early research where there might be a plausibility and a small cohort that show activity but they are predominantly focused on safety. And thus the whole process of early IND oversight is focused on safety.

And what goes into reviewing a gene therapy protocol? When a submission comes into the agency for the most part we have had discussions with the sponsors on the gene therapy protocols and what their intentions might be. We talk about the scientific challenges, some of the approaches they may take, some of the preclinical studies they may take.

We take into consideration if it has gone through RAC approval what the recommendations of the RAC have been and those all go into that type of decision making and discussion.

When an IND comes in through the FDA's door a time clock starts. We have a 30-day period in which to assess the safety and validity of the IND. And in this process what do we look at? We look at the product manufacturing. We look at the testing of the product. We look at its quality, safety and purity and potency. We may look at purification schemes and make advice in all of those areas.

We look at the animal studies. What are the

animal studies telling us about the safety of the product, about the potential biological plausibility of it having activity?   Those are all looked at in the context of the proposal of the gene therapy protocol.

The particular emphasis here is on patient safety. What can we learn from the animals that will help us to better predict how to monitor toxicities in humans when this particular product goes into an individual? This is extremely important. It will also help us in identifying dosing for the patient population, which is also an important part because we may have to lower starting doses as they go into humans.

We may also at this point in time as we review the protocols decide that additional animal testing is needed in order to have a better handle on what we need to monitor in humans.

We also may ask for modifications in the informed consent based on the data we have reviewed and we will ask that of the sponsors as they come in.

The agency will also look at modifications to stopping rules for these protocols to ensure that the trial will be stopped if certain adverse events occur with certain severities.

This is not a one time process at the FDA. This is real time activity. There will be changes made as the trial then -- if it is allowed to proceed -- as the trial starts to go down that road.

If, in fact, when the agency is reviewing an IND they have any concerns, major concerns on the safety of a trial, the trial will go on clinical hold. And this go on -- a clinical hold can take place if the initial study protocol -- we believe there are safety risks to the patients or after the trial is ongoing and certain adverse events take place.

So this is something that I think I will talk a little bit more about in greater depth.

As mentioned, adverse events are reported to the NIH. Adverse events are reported to the FDA. Sponsors must report all adverse events to the FDA in an annual report. However, in addition, an adverse event that is associated with a product that is both severe and serious and unexpected must be reported as soon as possible and no later than 15 days.

Also, if there is a life-threatening event or a death that sponsor must inform either by telephone or facsimile that that event occurred within seven days.

Any findings that we see in animal laboratory testing that may have a significant risk for humans must be reported to the FDA within 15 days.

So what happens when these adverse events are reported to the FDA? Well, when these adverse events are reported a number of things can happen.

The agency may decide to change the eligibility criteria to exclude patients at high risk. They may change the dose route of administration and the schedule of administration. They may change the informed consent to add -- to disclose the new toxicities. They may ask for additional consent from study participants to reflect the new information.

They request that the clinical brochure, clinical investigator's brochure be updated. They may require -- we may require that new nonclinical studies be performed and we may place the IND on clinical hold.

In addition, in taking all these actions, we may also put other IND's for related products on hold if we believe that those toxicities or events could have an impact on patients in other trials.

While a study is on clinical hold, no new subjects may be recruited and treated. Patients in the study are taken off the product unless specifically permitted to continue by the FDA based on particular circumstances.

So what has the FDA done recently as a result of the events that have surrounded the gene therapy trials and events that have occurred?

Well, as Dr. Skirboll says, we have increased communications between the FDA and the NIH. We have put standard operating procedures in place to give information on a weekly basis to the NIH on severe and life-threatening adverse events, serious and life-threatening adverse events, as well as protocol changes.

There is an enhanced communication on issues that may raise to a level of concern between the two agencies on both sides with respect to conduct of clinical trials.

An important aspect of conduct of clinical trials, which transcends not only the issue of gene therapy but all clinical trials, is having appropriate good clinical practices. In this regard the FDA has been working with an international forum, which is composed -- which is called the International Conference on Harmonization.

A number of documents have been developed on quality, safety and efficacy as a result of this process but of particular importance and relevance to this case is a good guidance document which is dealing with good clinical practices, which it talks about clinical monitoring, informed consent, et cetera.

These are very important documents. It lays out the responsibilities of the sponsor. It lays out the responsibilities of the investigator.

I think one of the aspects that is relevant in the gene therapy area that may impact on some issues that we are currently engaged in looking at is in the normal course of clinical trials there are distinct responsibilities for sponsors and distinct responsibilities for investigators.

Often times because many of the innovations in gene therapy have come out of academic institutions there may be the possibility and has a higher frequency of the investigator being the sponsor. In this case some of the checks and balances of the responsibilities may not be as strong when there are independent sponsor investigator relationships and that is one thing that we are looking at right now.

And I think it is important that those issues be discussed.

In addition, the FDA has a bioresearch monitoring program. The agency is going to be enhancing as resources permit our looks at clinical investigations underway, particularly in the gene therapy area.

We will do "for cause" inspections, which means when there are problems we will be in there looking at them but we will also be doing a limited number of inspections in order to see what the field is looking like independent.

Why are we doing that?

One, we want to see how these trials are being conducted looking at if, in fact, additional education, guidance, compliance issues are necessary in this area for further action.

In addition, the agency is moving forward with a proposed rule to enhance disclosure of specified material in gene therapy clinical studies. This will increase the public awareness of what is going on in this field.

We believe at the FDA that gene therapy is an exciting and innovative area of science. It needs to continue to go on and to be supported but it also needs to proceed with appropriate clinical monitoring oversight so that the safety of the patients are well cared for.

And in this, the agency is looking critically at the activities going on in these clinical trials.

We believe that this information is important in enhancing the fruits of the biomedical technology that is underway and the whole explosion of biomedical research and the promise that it brings but we believe that the safety of patients come first and as we proceed we must take good care to protect their rights.

Thank you.

DISCUSSION WITH COMMISSIONERS

DR. SHAPIRO: Thank you very much.

Let me thank all members of the panel.

I want to turn as quickly as possible to members of the Commission to see what questions they have. Let me just ask the Commissioners themselves when I recognize them to pick their most important question first and let everybody get around so we do not get -- so we all have a chance to ask what we think are the most important questions.

Alta, and then Larry.

PROF. CHARO: Thanks very much.

NBAC has over the years written reports that have recommended the creation of a national body to exercise review over special areas that pose special concerns. We have done this in the report on people with impaired capacity to make decisions. We have done it with regard to the report on embryo research and stem cell research.

And so this is an area that provides one of the few examples of that kind of extra layer of national review which differs from the usual kind of decentralized local systems so I would like to ask you to focus just not on gene therapy but just on the phenomenon of systems that have a national level.

You have described a system that has multiple local reviews, parallel federal reviews, special RAC recommendations, adverse event reporting to two separate agencies. I am interested in whether -- the Gelsinger experiment aside because I understand that adverse events occur in well-run experiments as well as experiments that are not well-run. I am not going to comment on whether I think it was properly done or not.

But, in general, do you think that the system as it now stands is working or is it failing and if it is failing is it because there are too many reviews that are conflicting with one another or is it because there are too few reviews or that the reviews are focusing on the wrong things?

This would help us use the example of the RAC and the extra reviews in the gene therapy area when we

begin to look again at whether or not centralized review makes sense in other contexts.

DR. SHAPIRO: Lana?

DR. SKIRBOLL: A good question.

First of all, let me point out that the history of the RAC is important here because the RAC, as we know, came from really the famous Asilomar conference in which scientists came together, saw legislation moving towards shutting down whole arenas of really important research, and it was recognized as the formation of the scientists recognizing risk and be willing to put those risks into a public discussion.

In that regard and, in fact, if you look at our guidelines for stem cells, we were very responsive to your point, where there is a new cutting area of research that holds for whatever reason some particular public concern such as gene therapy or stem cell research, the public discussion, I think from NIH's perspective and I hope from the scientific community's perspective, is vital to not only ensure patient safety but also to ensure public trust.

From that perspective it is important.

The guidelines themselves, I think, have been vital in helping IRBs and investigators understand

what the rules of play are. There has been, I think, a misunderstanding of the complementary roles of the FDA and the NIH. There has been a sense that RAC does or RAC or the NIH is responsible for real time monitoring of trials. It is not. It is responsible for the development of policy in a public forum around a cutting edge young area of research that holds enormous promise but still has risks.

From our perspective I think NIH feels that the RAC has had an important role but under that context of the state-of-the-art of gene therapy and particular public concerns.

PROF. CHARO: Let me put it this way: If you were asked today to design a system for gene therapy, would you design exactly the system you now have or would you design one that is different and, if it were to be different, in what way?

DR. SKIRBOLL: Well, that is hard for me to answer. I am in the middle of getting advice from a lot of people about how to do it better.

Is the system perfect? No, it is not perfect and I am not sure -- it is only because the system is not perfect or the public perception is not perfect. The goals and the mandated missions of the NIH and FDA in this oversight, I think, are correct. I would not change the goal. I would not change the regulatory authority of FDA over this area. They do a great job and they do it thoroughly. NIH should not be held responsible for regulatory authority over this arena.

We do not -- even when we had approval we never had the authority that FDA has to shut down a clinical trial the way an IRB does, to put a trial on hold the way FDA does, and that authority should not happen.

I am not sure we -- FDA -- the RAC has had discussions about could you create policy without reviewing protocols. Could you change the system that dramatically? And most of the RAC members, most of the advice we have gotten is that it is hard to create policy, important policy, germ line gene transfer, *in utero* policy, without undergoing the context of protocol review.

So I think I would make some changes in the process but I certainly would not reinvent it totally. I hope that is at least helpful.

DR. SHAPIRO: Thank you.

Dr. Zoon, quickly. We want to get to other questions.

DR. ZOON: Just a brief comment. I believe that the system that is in place now works. However,

if I were to have said for these new areas of science the importance of public discussion is, I think, critical for public trust as well and I think it actually enables the industry to move forward, to move the products to the patients because without that public trust there is not the ability to move forward in these areas.

Patient safety, of course, is paramount and when people do not follow the laws, the regulations, the guidance, it is clearly where a problem comes and FDA has to take action in those areas, and we have the authority to do so.

The issue always becomes are you resourced enough to do everything you have to do yesterday and I think that is one of the challenges FDA has on the resource issue area because we have the tools. The issue is do we have all the resources that we need sometimes to do these jobs.

DR. SHAPIRO: Thank you.

Larry?

DR. MIIKE: Harold, I practiced all last night getting ready to ask multi-layer multi-questions and you just cut me off.

(Laughter.)

DR. SHAPIRO: I am always ready for last

year's vacation, too.

DR. MIIKE: So I will stick to my usual mode.

I have a question on the RAC process. The change for an earlier RAC review -- I have got a lot of questions about that but my one for the moment is what does that say about the current process where an IRB reviews and RAC reviews? The way I read it now, IRB reviews and then RAC reviews.

What is the impetus behind an earlier RAC review? Is it because the IRB process has passed proposed projects that on RAC review has been found to be inadequate? What is the impetus for that shift?

DR. MICKELSON: Well, there are two reasons for the shift. One, that given -- since 1997 when the committee lost or the NIH Director gave up approval, the committee was receiving and reviewing protocols that had already been initiated so that the input and review by the committee members, which did have a great deal of expertise in drafting informed consent documents and the scientific review of protocols, was lost because the -- in some cases the protocols had already enrolled and treated patients.

But the committee at that time felt that there were issues that needed public discussion about those particular scientific protocols so our efforts

to move the protocol review to an earlier phase before patients could be enrolled and before institutional review boards had given approval was also based on the fact that when we would look at the informed consent documents there were some areas that could have been drastically improved in those cases where we looked.

We are only looking at 10 percent of the protocols that come into the Office of Biotechnology Activities and that is because it seems that only -- so far only about 10 percent have issues that raise to a level that at least three members of the committee wish to review them.

Also, moving the review process to an earlier step allows us to have a greater impact on the scientific quality of the protocols that we see.

Many of the protocols that we see because of the length of time it takes during development -- we see many protocols that, in fact, use almost essentially the same vector but in slightly different patient populations and given the history that most of the protocols are still in Phase I there are many important biological issues that are not being addressed and we would like to encourage greater scientific quality and use of the clinical trials so that the data -- and to -- for -- to urge the investigators to obtain more information from these trials and then use those back into basic science studies so that the next round of clinical trials that we see are better.

We have 390 clinical trials out there that change in the vectors. Each step is hard won and is minuscule but the public discussion and the input that can be got in that wider forum could really drive the science in a much better direction.

Also, the public discussion of the RAC in terms of informed consent issues -- when we have written these down and gone back to the local institutional review boards they have been very helpful to the local committees.

Many of the committees, both the institutional biosafety committees and the institutional review boards give approval contingent upon the decision of the RAC review. That does not -- they do not all but that leaves them some -- gives them some leeway then to incorporate the RAC recommendations.

But it was basically to stop the committee from reviewing protocols that had already started and enrolled and treated patients so that the public concerns and scientific and ethical issues could be gotten in at an earlier phase.

DR. SHAPIRO: Thank you.

Rhetaugh?

DR. DUMAS: My concerns are systems concerns as well. There is NIH, FDA, then there is OPRR that I see as major components of a system. I am not really quite sure how NIH and FDA conceives of that relationship with OPRR. That is one thing.

The other thing is given this system where, if any, are the mechanisms for real time monitoring?

DR. SKIRBOLL: Well, I think --

DR. SHAPIRO: Thank you. Well, Dr. Zoon, why don't you begin?

DR. SKIRBOLL: Yes. I was going to say Kathy should answer this one.

DR. ZOON: Right now we have an active interrelationship with OPRR as well with the FDA as OPRR, I think, recently just transferred to HHS out of NIH into the Secretary's office but we interact with OPRR on bioresearch monitoring issues as well as interacting with NIH on the other issues. Real time monitoring is done by the FDA.

Some of the issues that I described to you -- when we get a serious adverse event, all those things that we do and look at as a result of a serious adverse event that is unexpected and associated with the product will be dealt with.

We also get -- and those are dealt with on a real time. We will look at the protocol and make changes in that area.

DR. DUMAS: I am concerned about whether or not there is any possibility for determining an adverse event on the way to happening or do you deal with them always after the fact? I mean, are there ways to pick up potential problems in projects that could probably prevent an adverse event?

DR. ZOON: Yes. Just the preclinical data that we get in to support a study is designed to help the clinical investigators and the sponsors conducting the study to identify those toxicities that are present in animal models but those are animals. They are sometimes predictive in humans, sometimes they are not predictive in humans. They are a tool that develops a spectrum of activities that we study.

Once the study then proceeds to humans and you learn more then you add more factors into the protocol, more testing or clinical oversight of a patient based on those toxicities. So it is an iterative process that you constantly learn and modify with in order to assure the safety of the patient. So it is a very dynamic interactive process.

Lana, did you --

DR. SKIRBOLL: Yes. First of all, I want to just go back briefly. OPRR's responsibility is oversight of the system. They do not review individual protocols so what is different here, first of all, is the RAC and the FDA review protocols.

RAC review primarily takes place before the initiation of the protocol. FDA review is both at the initiation of the protocol and is responsible for real time monitoring as the protocol proceeds.

With regard to looking forward to potential adverse events FDA obviously keeps its eye on what is happening patient by patient and event by event in terms of preventing subsequent events. NIH in analyzing both data on adverse events can start to see if there is a trend line developing with adverse events happening with a certain dose or a certain vector.

So that goes back to the issue of the roles of these three oversight, NIH, FDA and OPRR, as I said before, are unique but complementary. They work together at various levels of the system to ensure patient safety.

DR. SHAPIRO: Rhetaugh, is this very short?

DR. DUMAS: Yes, very short. It has to do with whether there is any way for determining whether these adverse events are really actually reported.

DR. ZOON: On our inspections we look at the records. Often, as I said, we have very limited resources in the bioresearch monitoring but we do have mechanisms as we do those research monitoring to look at the adverse events at the site with the clinical charts and then monitor them with the consistency that has been reported to the agency in reports.

And that type of study is done -- there are about 1,000 bioresearch monitoring inspections at FDA overall in any given year because we are talking about the system now, not just gene therapy. Those sites are looked at for integrity of data through the bioresearch or the data integrity as well the validity of the data, which addresses, I think, how do we know what is coming in and is it good.

DR. DUMAS: Thank you. That gets at my concern.

DR. SHAPIRO: Thank you.

Tom?

DR. MURRAY: Thank you, Harold, and thanks to the panel for coming today.

I suspect most of us would agree certainly on

the Commission here, you and the audience that it is absolutely essential that public confidence and trust in the system of protections for participants in scientific research be as good as humanly possible. So the discussion is how to make that happen here, not so much to cast blame for what may or may not have been done with the Gelsinger case.

I should disclose that I am a member of this NIH panel working group that is looking at NIH oversight for gene therapy research so I got a heavy dose of gene therapy background on Monday.

Thinking about the case that has spawned -- sort of spurred this panel, one set of issues has to do with alterations in protocols and informed consent that may have taken place or that perhaps should have taken place and did not but I am not going -- I am going to leave those aside.

I am going to focus instead on a second issue which is the -- the unmistakable importance that scientists have full and up-to-date knowledge of the risks. So adverse events are about risks. That IRBs, the RAC or any other body reviewing the research for its ethical acceptability also have full and up-to-date knowledge of the risks.

And, thirdly, that -- and most importantly

that potential participants in the study be given full, complete and accurate information about the risks.

And I think one of the most distressing sequelae of the Gelsinger case is that it has come to our knowledge that many of the reports of potential risks were coming in marked and stamped "confidential," were -- there is a question about whether they -- all that information was fully shared with other investigators who were using similar procedures, perhaps similar vectors, routes of administration, dosages or whatever.

And a concern that no one body of scientists had the -- what we can call the big picture of what all the risks were and all these dimensions. They could then think about that and make sure that other scientists in the field, IRBs and subjects knew about the risks.

What can we do to assure that somebody has that big picture and that that information is communicated in a useful and a swift manner to all the parties of interest?

DR. ZOON: Could I comment?

DR. SHAPIRO: Yes.

DR. MICKELSON: I just wanted to comment I do agree with Dr. Murray. I think it is absolutely essential that adverse event data be in the public realm, that it be put in its proper context but having adverse event data and clinical results or results from the clinical trials in the public realm I think is absolutely fundamental to the future of the field.

While it may be different than is routinely done for any pharmaceutical -- other pharmaceutical field, access to information and exchange of information is fundamental to science. If this field wishes to have a rapid progress -- to progress rapidly that exchange will improve the clinical studies. It will make for better protocols. It will improve and reduce the risks for patients. They will understand what has gone on in other trials before they signed a consent form.

If we do this correctly it can be done while protecting industry's rights to protection for trade secrets and proprietary information. There is no wish to harm industry in all of this.

However, scientific information and the results of trials when put into an arena that patients and other scientists can access, that has been long recognized as -- it is equivalent to a scientific publication. There should be no reason to hold this information as confidential. It has been marked confidential when submitted to the RAC and we have fought through the Office of General Counsel to remove that label so that it can be accessed.

Also, the reviews of the RAC should be on the web and they are. And when people call, we tell institutional review boards, "If you were reviewing a protocol that uses vector X, Y and Z, please look at the RAC minutes on the web of this particular meeting and you will see RAC comments about protocols using similar vectors."

Now I have received calls but that is value added to public access. Institutional review boards and other scientists have an idea of what the pitfalls were for previous trials. There can be no doubt that that is valuable.

DR. SHAPIRO: Thank you.

Dr. Zoon, very short.

DR. ZOON: Yes.

DR. SHAPIRO: We are going to have to adopt some new rules here in a minute.

DR. ZOON: Very short. One point of clarification when FDA has a problem with gene therapy or any other therapy that it believes it transcends a given protocol, the FDA has the ability to identify other protocols as well as contact those and put those other trials on clinical hold, and that has to be done in real time to protect the patients.

The activities that the RAC does are very important for the broader bigger picture but the FDA must act quickly in order to make sure that patient protection is observed and that has to be done by the individuals that noted -- know the adverse event as soon as possible.

DR. MICKELSON: Right. Those are two different mechanisms.

DR. SHAPIRO: No, let's not have a -- okay.

DR. MICKELSON: Yes.

DR. SHAPIRO: Let's not have a debate on this.

I have five Commissioners who would like to say something and I would ask them each to be as brief as possible and, likewise, the responses.

Bernie?

DR. LO: Thanks. I want to shift the focus of attention for a minute. You have been talking about sort of what is novel about gene therapy and NIH has talked about how the RAC looks at things like *in utero* therapy and germ line therapy. FDA is talking about novel sort of vectors and viruses. But it seems to me that a lot of the problems that may be going on are not cutting edge. They are sort of old-fashioned.

And one has to do with the confusion between clinical research and clinical care, and the misperception that entering a Phase I/II clinical trial somehow is going to be therapeutic for that patient. And this is something this Commission has talked about in a lot of other contexts but it seems that here there is even more reason to have this misconception for many, many reasons.

Putting aside sort of the systems issues we have been talking about, how do we get at this issue of informed decision making and how do we work on both, it seems, investigators and potential participants to help them understand that certainly in the Phase I/II trials that are the bulk of what is going on according to your slide that this really is not therapy even though that doctor may be your doctor as well as the PI and the sponsor.

There is a whole mind set and a whole interaction process that really sets up the misconception and confusion and it seems to me all these sort of complex systems you have worked out or working out do not really get to that problem, which at least in the public discussion of this event adds confusion, and it seems to me again it is both on the part of the investigators and the potential participants.

DR. SKIRBOLL: Let me address that in two brief -- very brief ways. First of all, one of the things that the NIH Guidelines have done recently in this arena is changed the title. In every placed we have called it gene therapy, we have called it "gene transfer" research. It is not a therapy at this point so that is a misconception that we create ourselves by calling it a therapy.

Second of all, the informed consent document is probably the one thing that the RAC has looked at over the years and added to informed consent documents and made points is this the very point you are raising, is it made clear to the patient that this is -- this is a safety test, this is not a treatment.

But what this suffers from is a difficult issue because it is what I often call the "collusion of hope" between the patient and the investigator. If the investigator is describing the purpose of his research the long-term purpose of that research is obviously therapy. That trial may be about safety but the purpose of the research is therapy so somewhere in

the description of the research itself and the informed decision making of a particular trial there does need to be more effort to make sure the patient understands that this particular trial is safety, not efficacy.

And it is -- it is an up hill battle. Not ones that -- not one that I think investigators do by intent but by part of this collusion of hope. Both patient and investigator are looking for a new treatment but it is a difficult one.

DR. LO: Right. And so the question is given that collusion of hope what can be done on a systemwide basis to kind of make the decision making more informed?

DR. SKIRBOLL: Well, the RAC guidelines say clearly that informed consent in Phase I trials make it clear that this is a safety trial. This is -- this goes back to advice to IRBs to make sure that they are looking clearly at this informed consent -- informed decision making and that patients understand -- I do not have any other quick solutions to that. I do not know if my colleagues do.

DR. SHAPIRO: Thank you.

Alex?

PROF. CAPRON: The question that I want to

get an answer to has to do with what we have learned from this but I need clarification on one thing I just have not seen in the press and perhaps Dr. Zoon can supply this.

Dr. Varmus was quoted as saying -- in fact, in the letter he wrote, he said, "Of the 691 serious adverse events reported, 39 had been reported previously as required by the NIH Guidelines." And I have not seen any discussion in the press about the other 652.

Are we talking about events that had been reported to the FDA previously? Were these all from the prior year? Did we have 652 in the prior 12 month period? I just have not had any clarity on that and I do not understand the situation. If you could --

DR. ZOON: Okay. I think both Dr. Skirboll and I will need to clarify this because -- let me just reiterate briefly how the FDA gets adverse events. If there is an adverse -- a serious adverse event associated with -- that is unexpected and associated with the product, the sponsor must file a report within 15 days. If it is life-threatening or fatal they must call or send us a fax within seven days.

All other adverse events are generally reported in periodic reports but at least in an annual

report.

PROF. CAPRON: This language was 691 serious adverse events. Was that a misstatement?

DR. ZOON: Well, adverse events that are expected are not required to come in with a 15 -- an adverse event that is serious and expected does not have to come in, in a 15 day report.

However, maybe Dr. Skirboll could talk about NIH's because you are referring to Dr. Varmus and that really is the NIH purview.

DR. SKIRBOLL: Let me say this in one sentence, Alex.

What we were referring to here was data that had not been reported to the NIH. In analysis, all of this data had been reported in the time fashion to which it was required under FDA regulation to the FDA.

The noncompliance with reporting was to the <u>NIH Guidelines</u>, not to the FDA regulatory requirements. So with regard to real time analysis of those adverse events and patient protections that data had been reported to the regulatory agency.

So that is -- thank you for allowing me to clarify that.

Those -- finally, those 692 adverse events were adenoviral vector serious adverse events that had

occurred over seven years of therapy so there was also a misconception that it was 692 events in a single year. It was seven years of group data that we asked the community for as part of the retrospective analysis of adverse events related to the death of Jesse Gelsinger.

So thank you for allowing me to clarify those two important points.

MR. HOLTZMAN: May I --

DR. SHAPIRO: Steve, just a second. Steve, if this is really just information here, okay, because --

MR. HOLTZMAN: It is really to get perfectly clear on this. There are three levels. All adverse events, which come in, in the annual report; product related, 15 days; and then the subset of product related which are serious or deaths, which is the seven day.

The 691, does that refer to the first level or is it the third level?

DR. ZOON: What you are looking at is -- I hate to say this but it is actually apples and oranges to a certain degree because we are talking about different numbers, different procedures, and the dataset that you are talking about is the NIH dataset.

The FDA as -- in the cross collaborative studies that we have had with NIH to look at adverse events actually FDA had a very good correlation of receiving everything that NIH has received recently that was considered serious and unexpected, and those reports had come in.

It is the responsibility of our sponsors to report all adverse events but really to triage themes the most important ones that are coming in related associated with the product to come in most rapidly depending on the nature of the adverse events that there are so that they -- the agency then could take modifications in either the protocol or the informed consent or the clinical brochure.

NIH is looking at this in a different way for trend analysis and understanding large cohorts of data in which to give directions to the investigators in a broad sense to the field on how to proceed or what needs to be changed, and I would let Lana again speak to this.

DR. PATTERSON: I want to try to clarify some of the numbers and the universe of adverse events that have been reported.

DR. SHAPIRO: Could I just interrupt for a second?

DR. PATTERSON: Sure.

DR. SHAPIRO: Since I am a little worried about time here. I do not want to straighten out all this numbers business unless it is directly relevant to your question.

PROF. CAPRON: I think we have gone beyond the point where it is directly relevant to what I wanted to ask Lana.

DR. SHAPIRO: We will leave this for later then.

PROF. CAPRON: You stated in your comments that the area of gene transfer research is unique because of this responsibility to report adverse events to the RAC and, also -- I mean, to the Office of Biological Activities but I mean -- the great problem for Commissions like our's is we come flying into Washington every month or so and we try to come up with good recommendations for things and as Alta has already mentioned we have made recommendations vis-a-vis national oversight bodies and, frankly, the RAC and the Asilomar experience was on our lips as we did those sorts of things.

Now we hear that there are severe problems in the RAC not hearing from the FDA about these hundreds of adverse events over seven years that were apparently new to you, the way that they have been reported here, and that is only for adenoviruses, and I gather we have not had an equal beating of the bushes as to any of the other recombinant DNA experiments.

And yet in our reports we have -- while we have made three recommendations about national oversight, we have made ten or so recommendations about responsibilities of IRBs. It is already a responsibility of the IRB to obtain from investigators reports of adverse events and to report those to the agency sponsoring the research. So this is not unique to the RAC area. There are responsibilities to -- between investigators and between the IRB and the institution vis-a-vis adverse outcomes with ordinary research.

Now what I want to know is what confidence can we feel if in the area of research that has received without question over its lifetime the most public attention and the highest level of review, we do not have a comparable thing for RAC yet. In other areas we rely on the IRBs.

Has this given you any thoughts about what needs to be done vis-a-vis the IRB system, which is the more basic form of protection of subjects if for all we know, as far as I know, it was not -- are you finding that the IRBs at these institutions where these 652 unreported events occurred knew about them and had not told you about them or were they equally in the dark?

And, if so, what does this mean for what you think in your examination of the system and what changes -- because I do not care about -- you know, we are not here to look into the Gelsinger case.

I want to know what has this taught you? What changes do you think are necessary vis-a-vis the IRB system if there are these gaps in the area that gets the most attention? What about all the other areas?

DR. SKIRBOLL: Alex, I think it is important to understand that adverse events and monitoring of trials, of course, is the responsibility of IRBs but IRBs as far as I know are not required to report adverse events back to the funding institution, the RAC or the FDA.

PROF. CAPRON: Let me --

DR. SKIRBOLL: That is the responsibility of the investigator or the sponsor. Now IRBs oversight as they --

PROF. CAPRON: Yes.

DR. SKIRBOLL: -- IRBs oversight of these arenas, one would hope and expect that as investigators are reporting adverse events in trials that that is part of the monitoring role of the IRB in terms of advising the investigator whether a trial should proceed and whether it should be put on hold.

Keep in mind there are two other entities that have not been mentioned here today, important institutional and local entities. One is the institutional biosafety committee, which also plays a role here and, also, for Phase III trials data and safety monitoring boards that also do this -- play the same kind of role.

So in terms of local analysis of adverse events I have no reason to believe from the data that we have at this juncture that local analysis of adverse events, consideration of safety of patients at the local level is not functioning properly. This was a discussion of what was reported to the federal body.

PROF. CAPRON: And will your inquiries that are going on now tell you the answer to that question? That is did the local data and safety monitoring board, institutional biosafety committee and IRBs in the institutions which reported to you these 652 adverse events have knowledge of those events and had

examined them and decided that there was no need in those cases to make alterations in those protocols because I -- you are correct that the IRB is supposed to know.

I guess it still remains the responsibility of the investigator to make sure that the reports are passed along but we know from the inspector general's report that review of ongoing studies was an area where the inspector general signalled that the IRBs maybe have not been doing all that they should in terms of annual reviews and so forth.

If these data of the 600 and some cases go back over seven years, I wonder again during that time will -- have you found that the IRBs knew about these and had annual review as well as reports of the unanticipated problems which are supposed to be made on a real time basis as I gather.

DR. SKIRBOLL: We are conducting not for cause site visits different than the FDA. We are going out to institutions to make sure that institutions know of the existence of the <u>NIH Guidelines</u>, are following the guidelines, know what their roles and responsibilities are with regard to reporting to the NIH. We are not, the NIH is not, investigating IRB oversight.

Now with that said with regard to Penn., for example, both FDA and OPRR are doing those investigations but I still think it is important, Alex, to recognize that where there was noncompliance as far as we know at this juncture is with regard to reporting to the NIH Guidelines.

We have no reason to believe that both FDA and the IRB did not get this information and make appropriate changes to trials as they were proceeding as a result of this adverse event. To that answer is we still -- we still only have in all these trials and all these patients one death that was related to gene therapy. We have no reason to believe that gene therapy is any more or less risky than many other areas of clinical research so I do not think this is necessarily indicative of a faulty local review system. I think that should not be -- you should not take it to go that far.

PROF. CAPRON: When you say you have no reason to believe that the IRBs -- are you looking? That is what I asked you. Are you looking to see whether the IBC's, the data monitoring safety boards and the IRBs knew about this? It is a question.

DR. SKIRBOLL: That is a question perhaps you should address to OPRR. The NIH does not -- the RAC does not go out -- we have -- the investigators are responsible to report to us. We are going out and making sure they have processes in place but we are not investigating whether those adverse events went appropriately to the IRB. We do know they went appropriately to the FDA and that, where appropriate, FDA made changes.

PROF. CAPRON: My impression was until just recently or maybe still today OPRR was part of the Office of the Director but I guess --

DR. SKIRBOLL: When I say "we," I mean the RAC and OBA. I am not speaking for OPRR or the NIH in that respect.

DR. SHAPIRO: Okay.

DR. SKIRBOLL: So that is a different question. Sorry.

DR. SHAPIRO: We can pursue the rest of this.

We have two minutes left of this part because I do have other people waiting which we must -- other guests here.

Steve, you can use any part of two minutes.

I apologize to Jim and Trish. We will not get to your questions.

Steve, you have two minutes.

MR. HOLTZMAN: Yes. It is not a question.

It is a request that some of this discussion about the numbers and whatnot and then the plea for not having these things confidential I think comes from maybe a lack of understanding about how the system currently functions. All right.

There may be something special about gene therapy where this stuff should be immediately published but before we can get to that argument we need to understand and it would be useful, I think, to the Commission to understand if I had come to Kathy back when she was at CBER with IL-5 and I had an adverse event and someone else came down the path with IL-5, even if I did not publish my negative result, she would not have left them go ahead with their IL-5. Okay.

So I think if we could have some clarification of how it works with nonexceptional drugs, non-emotive drugs, all right, we would then probably get some clarification about where the public discourse about cutting edge emotive things should lead us to have different kinds of policies.

DR. SKIRBOLL: Can I just make one statement? I think blink and it is going to change because there is a RAC working group looking at adverse event reporting with the goal of harmonizing what is required by the RAC and the Food and Drug Administration so that we will not have the kind of confusion that you are describing.

DR. MICKELSON: I also think that if someone were to come along if there was an adverse event with an IL-5 construct and someone else came along with a protocol for another IL-5 that potential patient should know that something happened in the first trial.

MR. HOLTZMAN: What I meant was the recombinant protein.

DR. MICKELSON: Okay.

MR. HOLTZMAN: All right.

DR. MICKELSON: All right.

MR. HOLTZMAN: Why is it different? You cannot get to that question until you understand how it is dealt with in the non-emotive/non-highly charged, politically, rhetorically, emotional drug.

DR. MICKELSON: And that is something to look at for the whole context of drugs.

DR. SHAPIRO: That was quite a series of adjectives, Steve.

(Laughter.)

DR. SHAPIRO: Thank you very much.

I am afraid we are going to have to end it.

I really want to thank the panel very much.

Dr. Patterson, I particularly apologize for having interrupted you the one time you attempted to speak.

I apologize and thank you very much for coming here today.

Thank you all very much.

We want to now move directly now to speak -- go on to our next panel, which is implementation of the common rule under a certain situation.

And we have Michele Russell-Einhorn here from the Office of Protection of Research Risks.

Perhaps we could -- Michele, you can take a seat at some comfortable spot there.

PANEL II: IMPLEMENTATION OF THE COMMON RULE THE CASE OF REVISING THE EXPEDITED REVIEW CATEGORIES AND THE CASE OF THE CLASSIFIED RESEARCH RULE

MICHELE RUSSELL-EINHORN, J.D., DIRECTOR FOR REGULATORY AFFAIRS, OFFICE FOR PROTECTION FROM RESEARCH RISKS

MS. RUSSELL-EINHORN: Is this on?

DR. SHAPIRO: That is on and what we area dealing here with is the case of revising of the expedited review categories in the case of classified research, which is -- that is right. It is under tab 3E, as you can see, in your agenda.

MS. RUSSELL-EINHORN: Okay.

DR. SHAPIRO: I apologize for keeping you waiting.

MS. RUSSELL-EINHORN: That is okay. No problem. Maybe I can get you all back on time again.

Thanks for the opportunity --

DR. SHAPIRO: That would be great.

MS. RUSSELL-EINHORN: -- to be here. I was asked to address two regulatory actions relating to the Common Rule but what I wanted to do first was to go over some -- to go over the regulatory structure of the Common Rule and I apologize if what I am about to discuss is basic but it is a rather complicated system and I want to make sure that we all share the same understanding of how the rule works.

This is the federal policy for the protection of human subjects and it is a policy. It is not an enforceable mechanism until a specific agency codifies the policy. There are -- one of the handouts that you received from me is called "Attachment 2." I do not know if it is easily accessible.

DR. SHAPIRO: Yes.

MS. RUSSELL-EINHORN: But it is a list of --

in the first part of the agencies and departments that are signatories to the Common Rule and the second part is a list of the agencies and independent departments and agencies that are not signatories.

There are 15 agencies that have separate codifications of the Common Rule. The Office of Science and Technology Policy accepts the policy. The CIA is bound to follow it by executive order and the Social Security Administration follows HHS rules by statute.

Other than those agencies, no agency, department or independent agency is required to provide the twin protections of institutional review board review and informed consent for research conducted, supported or regulated by those agencies.

So, for example, we know that there are several agencies such as the Department of Labor, the Appalachian Regional Commission and others that do conduct research and those agencies are not required to comply with the federal policy for the protection of human subjects.   So that is the basic regulatory structure.

The two examples -- actions that I have been asked to discuss: One is called the "interim final rule pertaining to additional protections for human subjects in classified research," and that is what I am going to begin with.

You should have received in your handouts the President's Executive Memorandum dated March 19, 1997, and a copy of the Interim Final Rule that is being distributed to the agencies, the signatory agencies for signature.

Very briefly because I did give you a handout, the interim final rule would create the first amendment to the Common Rule. It would be a Section 125. It is in specific response to a presidential executive order dated March of 1997. That presidential executive memorandum called for additional protections for human subjects in classified research and is actually very, very specific.

It does not call for a discussion of what protections should be considered. It calls for very specific things such as a nonfederal member on the IRB. It calls for agency review of those decisions, et cetera.

We started off by drafting this as something called the "Notice of Proposed Rulemaking." That means that we would take a proposed rule, put it in the Federal Register, probably ask for comments during a period of 90 days, get those comments, review them, integrate them and then publish a final rule.

The problem is that we are dealing with the Common Rule and in order to change the Common Rule we have to have the 15 agencies that have separate codifications of it agree to the Notice of Proposed Rulemaking. So let's assume that 15 of you sitting around this table are secretaries or administrators of federal agencies and Dr. Meslin is OPRR.

And in our Notice of Proposed Rulemaking in paragraph D we have the words "written determination" and seven of the agency heads based on advice from their Office of General Counsel and their senior policy advisors believe that the words "written determination" really are worthwhile and should be in paragraph D and the other eight agencies disagree. You all want oral determination and so now Dr. Meslin has the job of figuring out how to mediate between these 15 agencies. It is not easy and it does not always work.

We actually were lucky on the Notice of Proposed Rulemaking to get a rule that we sensed people could agree upon. We did get nine agencies' signatures. We do not quite know what happened to the other six. Did they disagree with it? Did they just not have an interest in signing?

I did have discussions with some agencies that did not want to sign the Notice of Proposed Rulemaking because they do not conduct classified research and they did not feel that they should put their agency's signature on a document that really did not apply to the work of the agency.

In June of 1998 two things happened. There was a lawsuit brought by the International Committee -- let's see if I can get the name right -- the International Committee on Offensive Microwave Weapons -- seeking to have the NPRM implemented immediately. They want the protections. And this was defended by the U.S. Attorney in U.S. District Court and ultimately dismissed.

At about the same time the White House Office of Science and Technology Policy received concurrence from the White House to change the NPRM to an interim final rule because of the time it was taken to get agencies to sign off on this.

And so we took back the NPRM from the agencies. We reformatted it as an interim final rule and an interim final rule means that it would get published in the Federal Register. It would be effective immediately but we would still take comments on it so the public would have an opportunity for input and at a later date we would integrate and change the interim final rule if necessary.

We passed around the interim final rule for signature in January of 1999 so that is about 13 months ago and we now have nine signatures on the interim final rule. We have six agencies that have not signed. We have one agency that has suggested it may not sign because it does not believe it should be going forward as an interim final rule.

That is basically where we are at right now but let me give you a minute or two about the process we went through. OPRR has captained this whole activity. We have used the National Science and Technology Council Human Subjects Research Subcommittee as the vehicle for getting different drafts to the signatory agencies. We have gone through the committee time after time with drafts and asked for their input, asked them to take it, the drafts to the Office of the General Counsel, to their senior policy advisors. We have had to take comments from all the different agencies, integrate them together, get people to agree on them and so forth.

So to wrap up the discussion of the interim final rule, we started the project in March of 1997.

We need to get 15 agencies to sign off on this. We have nine agencies so far and we are waiting for signatures from six other agencies.

The other activity that involves the Common Rule is the 1998 revision of the expedited review list. The -- in 1981 -- so this is ten years before the federal policy was published -- the Department of Health and Human Services published a list of research activities which could be reviewed through expedited review procedures.

The Common Rule published ten years later incorporated by reference this expedited review list in Section 110 and, very briefly, expedited review of research is permitted if the research is no more than minimal risk and it falls within a category on the expedited review list.

It is very important to note that the fact that research can be expedited does not mean that it is easier to waive consent. All the other requirements of the Common Rule apply. I like to say it really only means that the number of people on the IRB who have to look at the research decreases. Other than that there is nothing different about it.

So who can change the expedited review list? This is a very different process than trying to have an interim final rule on classified research taking the form of an amendment to the Common Rule.

Section 110 in the Common Rule not only describes the circumstances under which an expedited review is permitted but notably it permits the Secretary of HHS to amend the list "as appropriate after consultation with other departments and agencies through periodic republication."

So there is no requirement that the other agencies codify the expedited review list and because of that this was a very different procedure. Over the years we had received suggestions about changing the expedited review list. We began the process in March of '97 around the same time the classified research rule activity began.

Again we used the auspices of the Interagency Human Subjects Committee as a means of getting comments on the drafts, as a means of getting draft lists to different agencies for comments, and we worked very closely with the Food and Drug Administration.

And not to get too complicated, there is two different lists actually. There is an OPRR list and an FDA list but I will be speaking generically in terms of the OPRR list.

We worked with the DHHS Office of the General Counsel. And, as noted in my handout, the sense was that we were not required by the language in the Common Rule to put this proposed list out for notice and comment.

We thought this would be a worthy addition to the process so we did so anyway and in November of 1997 only nine months after we began the revision process we published a proposed list for public comment in the Federal Register.

We had a 120 day comment period. We received 108 comments, which is quite different from the 22,000 comments, which I understand the Stem Cell Council has received. So the 108 were actually very easy to deal with. We revised them.

The drafts went back to the Interagency Committee, back to the agencies for comment, and then because OPRR only had to consult with the agencies we published a final list on November 9th, 1998, so we are really talking about a year and nine months from the time that we started the process.

To summarize, there have been these two actions recently. These are the only actions involving -- regulatory actions involving the Common Rule. One is an attempt to amend the Common Rule. We require -- we have to get the signatures of 15 agencies.

And the other process was different because the Common Rule within its confines set forth a very separate procedure that gave one agency the authority to go forward with the process.

So that is basically a brief overview of what has been going on for the last three years.

DR. SHAPIRO: Well, thank you very much and thank you, also, for very concise and appropriate review. It really highlights the differences and it is an important issue for us as we go forward and think about any modifications we might want to make, how we might go about making them, what is effective and not.

So I think these two cases are really very helpful to look at as examples and I really thank you very much for your very clear presentation and also for the material you provided for us. It was very helpful to look at this so thank you very much.

Let me now turn to the Commissioners for questions.

Any questions about this?

Larry?

DISCUSSION WITH COMMISSIONERS

DR. MIIKE: Can this nutty system be changed by a presidential directive or do you statutory authority?

(Laughter.)

MS. RUSSELL-EINHORN: I believe we need statutory authority but HHS General Counsel's office would have the exact answer to that.

DR. SHAPIRO: Rhetaugh?

DR. DUMAS: I know that OPRR does investigations on site. Do you routinely do inspections?

MS. RUSSELL-EINHORN: Well, this is a little beyond my presentation and Dr. Tom Puglisi is here, Division of Human Subjects Protections, and Gary Ellis is here, too.

DR. DUMAS: Okay.

MS. RUSSELL-EINHORN: So maybe if you do not mind if Tom comes up to help answer this question.

DR. SHAPIRO: Not at all.

DR. PUGLISI: We do not do routine inspections as does FDA. We will do an occasional not for cause site visit on the order of zero or one per year.

DR. DUMAS: Okay. Thank you.

DR. SHAPIRO: Thank you.

Any other questions from Commissioners on this issue?

Yes, Alex?

PROF. CAPRON: Since Dr. Puglisi is at the table may I ask you the question that I could not get an answer from Dr. Skirboll on?

(Laughter.)

PROF. CAPRON: Have you looked at the 652 or for that matter the 691 total reports of serious adverse events to know whether the IRBs at those institutions had received reports as required in their assurances and had taken whatever actions were appropriate?

DR. PUGLISI: Okay. Let me just outline what is required under the regulations in answering that question. Institutions are required to report to OPRR any unanticipated problem involving risk to subjects or others or any serious or continuing noncompliance with the regulations.

So it is likely that some subset of the 600 and some adverse events that were identified by the Office of Biotechnology Activity should have been reported to OPRR.

The only one that I can tell you for certain was reported to OPRR was the incident at the

University of Pennsylvania.

In general, it is OPRR's feeling that unanticipated problems are under reported to OPRR. We recently did an inventory of the unanticipated problems that have been reported to us over the last three years. We found that in all areas OPRR receives about one to three reports per week.

Now when you consider how much human subject research is being conducted, one to three reports per week coming to OPRR seems to us like significant under reporting of unanticipated problems. However, we have not done an inventory of all the unanticipated problems that went to individual IRBs or compared what was sent either to Office of Biotechnology Activities or the FDA with what was reported to us.

PROF. CAPRON: You can understand, I think, the sense of this Commission that to the extent that we are relying on IRBs and our other reports as bodies which will be able to respond to particular problems with subjects with diminished capacity, with the stem cell work, and so forth that the notion that the actual operation, how well IRBs are doing on this issue, is of great concern to us.

What I am concerned about as I hear this is we have already learned that despite the expectation, which I think is implicit in the <u>NIH Guidelines for Recombinant DNA</u> that there will be communication between FDA and NIH, and despite this fact that the FDA and NIH have now said that from now on they will make sure that communication does, indeed, exist, it did not exist and NIH was learning -- FDA was learning stuff that NIH should have known and did not know.

What I am concerned about here is the sense that now the Office of Biotechnology Activities is -- has learned things which have not apparently caused OPRR to go and say, "Which were the institutions involved?" Let's take this as an occasion to see how well their IRBs were operating, not in a punitive sense but just this is a window into the process and it is the kind of window -- we do not have a staff to do this sort of thing but it is a window that I would love to know someone has looked through and said, "Well, it turns out that although these 691 events were serious adverse events they did not qualify for the sort of things that required immediate reporting as unanticipated problems because they were known to be a risk and they are not a surprise."

DR. PUGLISI: That is --

PROF. CAPRON: Nevertheless, I gather they are supposed to be part of the annual reporting process. Even ones that are not unanticipated should be part of the annual reports that IRBs review.

Again a question if this is seven years worth of events were they reviewed by IRBs? Did they insure that the ongoing research continuing over a second year took into account in the level of risk, in the informed consent form these experiences that were turned in even if they were not in the category of they were serious adverse events but maybe not unanticipated.

These are the kinds of questions I would love to know before we write a report on the oversight process and either say we are pretty confident that it is going on or nobody knows whether it is going on.

DR. PUGLISI: That is a very, very serious concern and it is one that has concerned us as well.

We are beginning to look at the question that you have raised. I must tell you that it will take us a significant amount of time and a significant amount of staff power in order to be able to do that and I do not know how long it is going to take to examine all of those.

Secondly, I can give you some anecdotal information. I have conducted or have been involved with probably 40 site visits to institutions where we had identified problems over the last ten years.

I can tell you in every one of those site visits we felt that investigators were not reporting unanticipated problems to the IRB in a timely fashion. It is a problem everywhere as far as I can tell from the anecdotal experience that I have.

DR. SHAPIRO: Well, it seems --

PROF. CAPRON: Do you suspend assurances in all of those cases until they correct it or is that --

DR. PUGLISI: We have done that, yes.

PROF. CAPRON: But not in all of those --

DR. PUGLISI: Usually -- not in all of those cases. Usually we have found that in the context of many, many other problems. So that it has not been the catalytic event that caused an assurance to be suspended.

DR. SHAPIRO: I judge from what has been said both here as a result of this discussion and as well as what was said earlier today in the other discussion that that really is a problem.

I mean, it is just completely obvious in that we ought to -- we do not have all the numbers but -- and that would be helpful if we knew more but whether we have those numbers or not it is quite clear at least on the basis of what people have appeared before us that this is really a serious problem.

Tom, this is going to be the last question right here.

DR. MURRAY: Yes. Actually Tom Puglisi and Michele are welcome to comment on this but really I want to share with the Commission something I learned Monday, which is when one looks at adverse events there are at least three dimensions of appraisal.

One is seriousness and that is clear that is a continuous scale, that is pretty clearly true although we tend to chunk it into sort of serious defined some way and then life-threatening or fatal as a kind of additional category, and then nonserious. They tend to -- seem to -- seems to functionally be a three category scheme.

The second dimension was unanticipated. Alex has mentioned that.

Now, you know, unanticipated could mean, you know, if this one operational definition of unanticipated is something not included on the consent form. So if the consent form includes as one of the possible complications "death" that is not unanticipated. Okay. It is important to bear that in mind.

Number three, the third level is associated

with. And here the operational definition will be very important as well as will be the process. Who -- what counts as "being associated with the intervention" and what counts -- and who makes the decision whether it is associated with or not?

Those three dimensions of appraisal and their definitions will turn out to be very important in what gets reported when and to whom.

DR. SHAPIRO: I think that is clearly right, Tom, and thank you very much. That is helpful.

It is also -- something I have put in the back of my mind is when asked about these questions when people are actually dealing with this and having the responsibilities to deal with it, people referred a number of times to being under resourced in the area. That means to me that they see something needs to be done and cannot do it perhaps for good reasons.

I am not in a position to judge that and so it seems to me that, you know, the message we are getting here is pretty clear and straight forward.

Marjorie, before we break, do you want to say a word?

DR. SPEERS: Yes. I wanted to thank Michele for her clear, concise and crisp presentation and make sure for the Commissioners that you did not miss some

of the very important points that Michele made and if they are not clear then I would like you to quiz her on them.

The first is that she said that the Common Rule is federal policy. It is not regulation.

And make sure that that is clear and that you understand that, that the Common Rule becomes regulation when each of the federal agencies that has signed on to it makes its own regulation and then it becomes enforceable within those agencies.

And that the Common Rule now is silent on how changes should occur with the exception of the expedited category, which is one of the reasons that every time we want to make a change there is not a clear office or entity that has responsibility for it, nor is there a swift process procedure that allows that change to occur, and a good example has been trying to develop regulation for classified research.

If you -- if that is all clear to you, fine, then let's go to the break. If not, or if I have misstated then clarify it for me.

DR. MIIKE: Excuse me. But can I ask then if it is federal policy and not federal law, why do we need a law to change it? If it is a federal policy it was determined by some process other than statute.

DR. PUGLISI: The policy becomes regulation when a specific department or agency adopts it and codifies it in the Code of Federal Regulations.

DR. MIIKE: That is why I say can't there be a presidential directive that tells the departments you will do et cetera?

DR. PUGLISI: Well, we thought we had one with the presidential directive that essentially dictated the language that should go into a modification of the Common Rule for classified research.

This is the easiest possible scenario for changing the Common Rule. The President says you are going to change the rule and you are going to change it in this manner and dictates the language.

Even under that best possible scenario it is taking us over three years to get that change implemented.

So I guess the answer to your question is theoretically the President could order each agency or cabinet secretary to make the change. In practice it does not happen very quickly.

DR. SHAPIRO: Gary, you had a brief response?

DR. ELLIS: One brief response. A direct response to Larry's specific question. In 1996, I personally begged the White House Domestic Policy Council to make the classified research change by presidential order and the White House legal counsel said they did not believe they had the authority to do that and that is why they went this route.

PROF. CAPRON: But isn't it true that that is not an issue of a statute restricting -- the national -- the 1974 National Research Act requires institutions to establish IRBs and it puts certain requirements vis-a-vis the informed consent.

But the regulations that were then in place and were put in place in the '80s and then the 1991 Common Rule are the result of agency action and collectively known as the Common Rule but as has been said for each agency binding when the agency -- the secretary or the agency director signs off on them but those are changed without requiring statutory action.

So your question is a good one. It does not require a statutory change for that to be achieved.

Why the President just does not pass it around in a cabinet meeting and say, "Why don't you all -- look, I am passing this down, sign it and pass it back to me," is another question.

(Laughter.)

DR. ELLIS: I asked.

(Laughter.)

DR. SHAPIRO: Well, thank you very much and thank you all very much.

We are going to take -- Eric wants to make a brief announcement and then we are going to take a 15-minute break.

Eric?

DR. MESLIN: For the several journalists who are here today in the audience who would like to spend a few minutes with Dr. Shapiro and I at the break, you are welcome to do so, so that we can respond to questions about the oversight report in general.

Journalists can meet in the registration table and we will take you to the room where that opportunity will be available to you and we will come back at --

DR. SHAPIRO: Fifteen minutes. Let's try to make it at a quarter to. Thank you.

(Whereupon, a break was taken.)

DR. SHAPIRO: All right. I would like to get this part of our meeting underway. At this early time in the morning we are already on our third panel so thank you very, very much for being here. We appreciate your presence.

Let me turn to Marjorie to introduce this panel.

Marjorie?

DR. SPEERS: Thank you.

Just to remind the Commissioners, the purpose of this panel is to learn about two alternative regulatory systems, two alternative oversight systems.

Both of these models were referred to in John Fletcher's paper to the Commission when you were considering the placement of OPRR.

The first panelist today is Diane Flack. She is with the Nuclear Regulatory Commission.

And our second panelist is Jane Ley who is with the Office of Government Ethics.

We are going to hear from both of them about their structure and function and then we will open it for questions.

DR. SHAPIRO: Thank you very much. I take it we are going in alphabetical order unless there is some reason to do otherwise.

Ms. Flack?

PANEL III: ALTERNATIVE FEDERAL REGULATORY SYSTEMS

DIANE FLACK, M.S.

SENIOR HEALTH PHYSICIST, RULEMAKING AND GUIDANCE BRANCH OFFICE OF NUCLEAR MATERIAL

SAFETY AND SAFEGUARDS,

NUCLEAR REGULATORY COMMISSION

MS. FLACK: I am not sure -- is this on?

DR. SHAPIRO: Yes, that is on. That one is on.

MS. FLACK: Okay. Good morning. Thank you for inviting the Nuclear Regulatory Commission to speak today.

I want to point out before I go any further that I am speaking as an individual. The management at NRC has not looked over my viewgraphs, talked to me about what I am going to say. I guess there is an element of trust and empowerment there. I do not know whether that is good or bad but anyway I just want to make sure that you are aware of that.

(Slide.)

As was noted, I am with the Nuclear Regulatory Commission. I am a senior health physicist in the Rulemaking and Guidance Branch, which is very appropriate for your topic this morning.

I was a member of the task group that developed Part 20, which is the Radiation Protections Standards that NRC uses. And I am a currently a member of the working group that is revising our medical use regulations.

(Slide.)

I am pleased to speak today on NRC's regulatory structure for ensuring the safe use of nuclear materials in the United States and, in particular, to touch upon two issues that you asked to hear about, the relationship between NRC and other federal agencies, and on how NRC regulations are developed and enforced.

To cover those topics this is a brief outline of how I propose to cover it.

(Slide.)

It is actually a pretty clean way of regulating. It started out with the Atomic Energy Act of 1954 which empowered the Atomic Energy Commission to establish rules, regulations and standards to govern the use or possession of nuclear materials as deemed necessary to protect health or minimize danger to life or property.

In the early '70s the Atomic Energy Commission came under increasing attack for its dual responsibilities for both regulating and developing the nuclear technology.

The question arose of whether they should create separate agencies to promote and to regulate civilian uses of nuclear energy and this concept gained particular support during the era of oil embargo and energy crisis of 1973-74.

As a consequence of that President Nixon responded to the energy crisis by asking Congress to create a new agency that could focus on and presumably speed up the licensing of nuclear plants.

(Slide.)

Therefore, the regulatory authority was transferred to the Nuclear Regulatory Commission by the Energy Reorganization Act of 1974, as amended and that is the basis for our regulatory authority today.

In order to carry out that regulatory authority NRC has developed a mission and that is on this vugraph. "The regulation of the nation's civilian use of byproducts, source and special nuclear material..." and then the same words that were way back in the Atomic Energy Act "...to ensure adequate protection of public health and safety to promote the common defense and security and to protect the environment."

One of the things that you will note is that this is a very narrow regulatory basis and authority which makes it very nice for us.

(Slide.)

How do we accomplish this mission? We have several different components.

One is the licensing process for nuclear facilities and also the licensing, the possession, use and disposal of nuclear materials.

We have the development and implementation of regulations to govern those licensed activities.

We have the inspection program and we have enforcement programs to assure that there are -- the licensees are compliant with these requirements.

(Slide.)

The NRC regulations are found in chapter 1 of Title X, which is "Energy" of the Code of Federal Regulations. Your particular interest would be in a part of Title X, part 35, which contains the regulations for the medical use of byproduct material.

These regulations are binding on all persons and organizations who receive a license from NRC to use nuclear material or operate facilities.

(Slide.)

How do we develop regulations? We have a standard rulemaking process and one of the main focuses on this rulemaking process, and it becomes more and more so every year, is to involve the stakeholders.

With the Part 35 example that we are

currently working on we started to involve the stakeholders, essentially the entire medical community that would be impacted by the changes in Part 35, way before we even put pen to paper.

And we -- in the old process you had one set -- one opportunity for public comment when the proposed rule was published but that is no longer the case. We involve the stakeholders all the way through. I think this is very, very important and it has worked very well with the development of our medical regulations.

Under the standard process we do have to have an identified need, though, before we can initiate any rulemaking and then we have to develop a plan for the rulemaking. We develop a proposed rule. It has to be approved by the Commission. It is published in the Federal Register for a public comment and then we develop a final rule.

(Slide.)

I think this is important. These are some of the needs for rulemaking: Petition for rulemaking from licensees, from private citizens, whatever. In the Part 35 rulemaking we have addressed a petition from the University of Cincinnati. User need memos, Commission directors, EDO directives, congressional or executive branch.

So there are multiple ways that we can -- multiple reasons why we initiate a rulemaking.

(Slide.)

How are our regulations enforced? There are two different programs. One is the inspection program and the other one is the enforcement program.

The inspection activities are primarily carried out in our regional offices and there are four of them throughout the United States and the enforcement functions are centralized in headquarters in Rockville.

When our inspectors go out to visit the licensees they are looking for violations. They are looking for them for several reasons, not just to, you know, to fine licensees but rather they are used as a deterrent to unsafe practices and use of radioactive material, and also to encourage prompt identification and prompt correction of the practices and procedures that led to the violation.

We have three different enforcement sanctions that we can use for those licensees that do not follow our regulations. Notices of violation: that just basically notifies a licensee that they do have a violation.

Civil penalties or fines and orders. There is a large range of orders that we can use. We can impose civil penalties. We can have a licensee modify, suspend or we can even revoke their license, or the order just might require corrective actions.

So that is essentially what NRC does. As I said, we have a clean authority. We have a clear set of ways of developing regulations, inspecting against them and enforcing them.

(Slide.)

The other part that I was asked to talk about was the relationship between the NRC and other federal agencies, how we work with other federal agencies. One of the ways that I picked out are MOUs. We have MOUs with a number of agencies.

Probably the one of greatest interest to you all in this room is the one with the Food and Drug Administration, where we share information on medical devices, drugs and biologic programs.

As you know, the FDA is responsible for assuring the safety and effectiveness and proper labeling of medical products, including drugs, devices and biologics.

NRC, on the other hand, is responsible for licensing and regulating nuclear material and

facilities.

Some of the things that we do as a result of this MOU is to inform each other of potential health problems. For example, malfunction of devices. We share information on new technologies and we have an annual meeting to discuss any other issues.

(Slide.)

Another way that I think is a very good model for agencies to work together are interagency committees.

For ten years, from 1984 to 1985, the Science Advisor to the President established the Committee on Interagency Radiation Research and Policy Coordination. I was fortunate to be on that staff for ten years. That committee was set up under the Federal Coordinating Council for Science, Engineering and Technology.

In this example, you take every agency that has an interest . In this case, radiation issues. It was very broad. In your situation it would be a much smaller -- more narrow focus.

There were 18 member agencies in the Federal Government that belonged to the committee and supported the committee.

What did it do? It coordinated radiation

matters among the member agencies, evaluated radiation research and provided advice on the formation of radiation policies. It was a neutral forum where member agencies could resolve radiation issues to best serve national interests. I think it worked very, very well. A good model to follow.

(Slide.)

There is currently a follow-up to the CIRRPC committee, another interagency committee. It is a little smaller. It has several -- seven member agencies. This one is called "ISCORS," Interagency Steering Committee on Radiation Standards.

There were seven agencies, but then I noticed last night, in 1998 they added another one, the Department of State.

It has similar functions to what the CIRRPC committee did and that is to foster early resolution and coordination of regulatory issues associated with radiation standards.

Some of the objectives were to use consistent and scientifically sound risk numbers and use risk -- scientifically sound risk management approaches in setting and implementing standards for occupational and public protection.

So those -- I think that is a good way for different agencies to work together.

The other one that is not on there is something that might be patterned after the federal guidance. The federal guidance for radiation protection standards is housed in the Administrator of the Environmental Protection Agency. It requires sign off eventually by the President but it involves all of the agencies. So that would be a third model that you might follow.

I brought a couple documents that I am going to leave with the Commission. A couple of them are just information on the NRC and the regulatory process.

There is a history of regulation, "The first 25 years of NRC." There are two documents on the two different interagency committees and one which -- unfortunately it is my only copy right now but I would be glad to have them xeroxed -- is a document that I co-authored which are across the board radiation protection standards and guides.

The reason why you might be interested in this is it provides the legal and the technical basis for the standards and regulatory authorities for all of the federal agencies that have to do with radiation.

DR. SHAPIRO: Well, thank you very, very much.

I would ask Commissioners really to hold their questions until we hear from the other member of the panel. Then we can address our questions to either member of the panel.

Ms. Ley?

That is it. You are on.

JANE LEY, J.D.

DEPUTY DIRECTOR FOR GOVERNMENT RELATIONS AND SPECIAL PROJECTS

OFFICE OF GOVERNMENT ETHICS

MS. LEY: Well, I am very pleased to be here this morning to talk to you about the structure that the Office of Government Ethics has in place for the Executive Branch Ethics Program.

And I feel that many of the experiences, both good and bad, that we have had over the last 20 years may be of interest to you because we have sort of gone from one kind of program to another over this period of time.

Let me give you just a little bit of background. The Office of Government Ethics is a small federal executive branch agency established by Ethics in Government Act, so we have a statutory basis.

The purpose in the Act said we are to provide overall direction of executive branch policies related to preventing conflicts of interest on the part of officers and employees of the executive branch.

Basically we are a policy development and a prevention program office. We have some limited enforcement powers, but we are not an enforcement agency per se.

At the time the office was created there were already in place a set of criminal conflict of interest statutes that had their basis in the Civil War period and beyond, and if an employee's conduct was egregious enough it would be prosecuted by the Department of Justice as a crime.

And more importantly, I think for your experience here, there was a set of administrative standards of conduct for all officers and employees, and those were standards that agency heads were required to have their employees adhere to and the penalties for that would have been reprimand through dismissal.

So they were -- it covered a much broader range of misconduct. Not something that you would get thrown into jail for doing, but something they just did not think at least executive branch employees should engage in that kind of conduct.

These came about in 1965, the basis for those administrative standards of conduct was a 1965 executive order. The President Lyndon Johnson issued this order.

It started in the Kennedy -- when President Kennedy was still alive, but it was actually issued by President Johnson and he directed the then Civil Service Commission, which is now OPM -- it is the federal agency responsible for personnel issues -- to issue a set of model ethics regulations based on the principles that were in this executive order he issued.

Those were issued and I think that they were about four pages long. Every agency of the executive branch was then told they could write their own regulations based on that model. They could not be inconsistent with it, but they could be more extensive and each agency would then interpret and enforce their own regulations.

Now, as you can imagine, there became -- there was wide disparities in the interpretation and enforcement of the very same words, agency by agency. I mean, in the area of gifts -- now over a few years

I should say -- in the area of gifts we would have an agency saying, "No, you cannot take a cup of coffee," and another agency say, "Sure, you can go on the QE II as long as you make a presentation at some point along there and take it all," using the same words.

In 19 -- basically as a result of Watergate -- I think we were created as a response to “you have got to do something more than just prosecute people.”

You have to try to get out there and do some prevention as well and make it more clear to employees what the standards are or what should be the minimum standards at least for federal service, and that is why OGE was created.

I have to tell you initially I -- I have been there since the beginning. We started out all in one room so we did not have much resources to do this for then three-and-a-half to four million executive branch employees. But what we did do was put together a basic structure for how we thought the program ought to work.

Basically we said we are not enforcing these rules in the executive branch. We do not have that authority. We said every agency head is responsible for the enforcement of the rules in his or her agency

and I think that as a management tool is the exact same -- is the exact thing to do because you must make that agency head responsible.

If you take that authority away, you also take the authority away from the agency head to actually have any control over the kind of conduct that you were trying to prevent.

Now we did not expect the agency head to do the day-to-day program, so we also said every agency head had to pick an ethics official, a primary ethics official with which our office would work and we would then run the executive branch program basically through the ethics officials. And the agency had to provide the resources to make sure that it was running properly in its own agency.

We basically -- let's see. In our area we decided there were four major things that we would be doing and we still do those today. We set the policies. We write rules and regulations and we make recommendations for statutory changes. We provide guidance and interpretation of what those policies -- you know, those regulations and rules-- are.

We provide it to the ethics officials and the ethics community and we provide it to employees when they find us. And the phone directory, they kept losing us for years, nobody could, you know, publish -- the Bell Telephone said we did not or whoever, the phone company said we did not exist.

We provide training and education programs for the ethics officials, and we then try to develop some training and education programs that ethics officials could use to get -- to train their employees.

And, finally, we would -- when we finally got enough authority, or not authority -- we had the authority to start with. It was the resources. We started to go out to agencies to see if they were actually doing what we were telling them they were supposed to do, so we started evaluating their programs.

So that is the basic structure of how our office was -- we envisioned the office to work and it really has not changed over the last 20 years.

Initially, however, when we were created we had to throw most of our resources toward giving guidance on a new post employment law and establishing a financial disclosure system, which I am sure many of you would prefer we had not, but we have, and we are required to do that. But what we found is that agencies were still all over the lot about these 1965 regulations they had in place.

So in 1989 when President -- as part of the -- well, actually as part of the election campaign, President Bush -- then President Bush basically said that he would -- he wanted to have one set of standards of conduct for the higher executive branch.

So in 1989 by executive order we, OGE, were directed to write one standard set of standards of conduct for the entire executive branch. Agencies could make additions to that but they could not change it in any way and additions would be, for instance, if an agency has a specific statute it would say that employees of that agency may not hold telecommunications stock.

We would allow them to make an addendum to the standards of conduct saying “and for the FCC you cannot hold that.” All those regulations had to be approved by us first and they are all published with ours. They are not published elsewhere so people cannot find them.

We issued a proposed regulation -- well, first of all, we started with a number of meetings with all the ethics officials. We tried to get some sense of where everybody was. We had a new executive order. We finally issued a set of proposed regulations and we got over 1,000 comments. Most of which came from inside the government but some of them did not.

Some of them came from the outside because, of course, we were dealing with gifts and outside responsibilities. Things that -- it was the conduct of the federal employee but there was a second party involved in the conduct and they were on the outside and they had comments they wanted to make as well.

We took into consideration all those published comments. We again had a number of meetings with ethics officials and other interested parties and then we finally published the final standards of conduct in 1993 and they became effective in 1993. We published them in the summer of 1992 and gave everybody six months to try to get their employees up to speed.

And then we put on a big push for training and education and then reviewing agency ethics programs.

Again the agency head still remains responsible for the -- how the program is run in their agency and if the program is not run properly, if we find it is not being run properly we can, after certain steps, issue corrective action orders to the head of an agency.

If the head of an agency does not do anything about it, at that point we go to the President publicly about that agency that is not complying.

The same is true if an agency is not properly -- is refusing to take action or cannot take action for some reason with regard to an individual employee. At that point we have to go to a public hearing and we have to have a public hearing about the conduct of the individual employee and we still simply make a recommendation to the President.

We cannot take any action, but we have never gotten -- we have never had a public hearing about an employee -- and we have had a few corrective action orders issued to agency heads but we have never had to go to a President, because no agency head wants to have it trumpeted that the program -- the ethics program in his or her agency is in the tanks.

We have the additional -- in terms of enforcement we have the additional benefit, I assume, because of the kinds of statutes that -- and regulations that we deal with, and maybe you as well, that challenge to agency actions by outsiders based on violations of these standards of conduct also bring these issues to a head so we see that as well.

How do we know whether the rules need to be changed or need to be adjusted? How do we get our input for our policy decisions? We have continual contact with the agency ethics officials.

We have training and education seminars with them. We have -- we call them brown bag lunches. We bring the ethics officials in and have issue discussions.

We get direct requests from agencies about where they think the rules do not work any longer or not properly.

Congress occasionally changes the statute which requires we have to occasionally change the rules.

And believe it or not, changes in technology have pushed on our standards of conduct and we have also had to make changes there as well.

It is a decentralized system. Again we do not have much enforcement authority but we do -- we are the policy setters. We do have the President behind us through executive order and we do -- and as an office we were created by statute.

I presume the President -- whether we were created by statute or not, I assume the President could have established us as a part of his -- some group within the White House given his basic authority to deal with the conduct of federal officials.

So those were the ways in which we got going.

DISCUSSION WITH COMMISSIONERS

DR. SHAPIRO: Thank you very much and once again thank you both very much.

I have a number of questions but let me just see if there are any questions from members of the Commission for either one.

Alta?

PROF. CHARO: Thank you both. This is very helpful as we look at the various models of regulation.

Ms. -- is it Ley?

MS. LEY: Yes.

PROF. CHARO: Ms. Ley, I wonder if I could ask you to expand a little bit on one aspect of your relationship with the agencies themselves.

You said that enforcement of the rule is still left with the agency heads and that the agency heads are also responsible for providing adequate resources for that enforcement function.

Historically, what has been the experience with OGE's success at having agency heads, in fact, enforce as vigorously as OGE might like to see and providing the resources OGE thinks are necessary since OGE has no direct line authority over the agency heads or the departmental secretaries?

MS. LEY: Actually we have had a fairly good history with that simply because nobody -- no agency wants -- as I said, no agency head wants to be considered to be running an unethical shop.

Now if we were enforcing some fiscal responsibility that might be different. You could argue that I am -- you know. But when we say the agency head is responsible for enforcement, it is because these statutes deal with individual personal conduct like an employee.

Do you reprimand an employee for -- you know, whether it is an ethical violation or you are incompetent or you are not -- you are not -- you know, an EEO or something. We think that really belongs with the head of the agency.

We try to do, to the extent we can, we survey agencies every year about the kinds of enforcement actions they are taking just to get a sense of whether we see nobody is doing anything or not and then we send these teams in once every three years to do a review of the program.

We have not found -- we have found one agency that tanked just because they took all the resources away from the ethics program. The program tanked, and that was the Department of Agriculture, and we went in there and they have really beefed that back up.

Most of the time the problem is resources because this is an internal structure program and when you cut the resources of an agency they take it out of training, they take it out of personnel, they take it out of everything but programs, and since the ethics -- the ethics part is in that hidden cost it gets hit.

We do try to watch it pretty well and we actually have a fairly good relationship with the DAEOs or the ethics officials. We call them DAEOs, Designated Agency Ethics Officials. They will tell us when they are getting cut. And so if we need to go talk to an agency head, we do.

So it is pretty good. They have been pretty good at enforcement.

DR. SHAPIRO: Thank you.

Alex?

PROF. CAPRON: I have a question for each of you. I think a common theme in the presentations has been the ability to act that arises when you have responsibilities and connections with departments but you can act without waiting for them all to sign on. You were probably here when we heard an earlier presentation about the difficulty of getting the Common Rule modified.

The question for Ms. Flack is in the description that we have from, I guess, your NRC web page there is a statement that the NRC was created as an independent agency by the Energy Reorganization Act of 1974, which abolished the Atomic Energy Commission and moved the AEC's regulatory functions to the NRC.

And what is implicit but not explicit there was the reason for that movement of taking the agency, the Atomic Energy Commission, which had had the dual responsibility to regulate and to promote the field of atomic energy, and to separate out the regulatory aspect from the promotion aspect which went to the Department of Energy.

Do you -- is that history important in the operation of the Commission today or is that unimportant today?

MS. FLACK: No. I think it is absolutely very important in the Commission today. There is essentially not even an office of education within NRC. I mean, it is strictly regulatory and all the programs are geared toward development of regulation, inspection, enforcement.

And the reason I am noting this is that when I was on the staff of the interagency committee, we were trying to find either in NRC or within DOE, which used to be ERTA, an office that was continuing the function of education. Education can be interpreted as promotion, and we definitely did not find anything like that in NRC.

You know, I am all for education. I was a little discouraged that that function was no longer there but, yes, it is taken very seriously. I mean, we are strictly tied to the functions that I mentioned. Yes, there is no -- the only research that is supported by NRC is to back up decisions that are made for licensing or inspection or something like that. There is no absolutely no R&D or education.

We do have very strong annual ethics training at the agency and I think probably it is so strong because we are a regulatory agency and discouraged from taking more than even a cup of coffee from a licensee or anything, so we do take very, very seriously the work of your committee.

PROF. CAPRON: The question for Ms. Ley is clearly you are in a position from what you have described and I would take from the description in the materials we got of the role of the committee that you can even get more deeply, it says, in limited circumstances investigate possible ethics violations and order corrective action.

You are in the position where you could be seen as a real annoyance by some of the departments and agencies and the implicit threat to go public with a statement of deficiency.

How -- what kind of protection do you feel you have from that kind of retribution within the government structure? You are a small office. Are there, through reporting lines to Congress, in terms of any committee that is seen as having authorizing authority over your area or appropriation authority in your field, are there sufficient ways that there are those who say this is an important activity and we want to make sure it goes forward, or are you fairly exposed to the political whims and get buffeted a lot by that?

MS. LEY: I would say that thanks to Congress for misnaming us as the Office of Government Ethics instead of something like Standards of Conduct that we are not very exposed to, you know, being done away with.

We were initially exposed early on to

budgetary cuts when we were part of OPM. When OPM needed money they thought they would take it -- they just took it out of our account. That is why we became a separate agency in 1989.

We have not really had in my experience since -- and I have been there since it was started -- it has been pretty much political hands off for us because of the subject we deal with.

And I will be very blunt, we have also had very good working relationships with the Council to the President for 20 years because one of the things that we have to do and that they need us for is we review all the financial disclosures of all presidential nominees before they can have their confirmation hearing, and committees will not have confirmation hearings for appointees until we have signed off on the conflicts issues of the financial disclosures.

I have never under estimated that little stick, club that we have in any administration, but -- so we have had fairly good working relationships with everyone. We have tried not to abuse our, you know, David-like authority and we have not had any Goliaths hit us either.

DR. SHAPIRO: So you are the people I have to

send all those forms to?

MS. LEY: Yes.

(Laughter.)

MS. LEY: I tried to keep that as quiet as possible but now I am exposed.

DR. SHAPIRO: Larry?

DR. MIIKE: I am just trying to relate your office's experience to what we might adopt, so I have several questions.

But the way I understand it, is that the way you monitor is that you go to the specific agencies and see what their paperwork looks like. You do not go out and go to my house or his house or anybody else's house and see whether what we have put down is true or not.

Second of all, you said you had an educational function and I assume that is going to the ethics officers in the separate agencies or departments and training them.

What is the size of your budget?

MS. LEY: $9.1 million.

DR. MIIKE: Because what I am trying to relate that to is that if we adopt a model such as your's, I do not think that we would be satisfied where we would depend on the agencies and we just do a

paper chase at the agencies and that either your office or the agencies themselves would have to reach out into the field, and that is why I was interested in the relative size.

DR. SHAPIRO: Carol, do you have a question?

DR. GREIDER: I think my question is somewhat similar to what Larry just said. It seemed to me that in the two presentations that one of the differences between the two models that we are thinking about is that the NRC oversees things that are out there and that the public is doing. Whereas your office will oversee things that are within the government, and that may make the two models very different.

So again similar to what Larry was saying, do you think that the kind of operational procedures that work so well for you at the OGE would work if there was this component that was not just within the government but people out there funded by the government?

MS. LEY: Well, it could. I mean, what you would have to do is not only set up a structure -- now I am just now talking off the top of my head, but it would seem like you would set up a structure where you have the person who is responsible for the in-house, but then they would also be responsible for then the

next level of training, the next level of review just like you review -- I assume you all review grants or agencies who give grants to people who do research, and get -- review those to see that they are complying with all sorts of regulations and this would be one of them as well.

If I may, Ms. Flack deals with an enforcement program and I deal with a prevention program basically, and we have fought to get more -- to not be given more enforcement powers. We do not want them. We do not want the cop and the counselor in the same office and we do not want that because we are lucky enough to already have a whole system of inspector generals. There is an investigative force out there in the government. We do not need one. And the FBI.

We have a whole administrative procedure about employee, you know, misconduct and it is already out there. We do not need to be a part of that. And we have the Justice Department prosecuting people. We do not have to be out there.

So we are -- we benefit by the fact that all those elements still exist. We just are not the ones that have to do them. We work very closely with the inspector generals and the Justice Department, though, to ensure that the rules and the statutes that we

provide guidance on, that they are interpreting them the same way, and they are very supportive of us in the way they take prosecutions, et cetera.

DR. SHAPIRO: Thank you.

Ms. Flack?

MS. FLACK: Yes. You made the statement about we are out there and that is true for most of our licensees. However, there are multiple federal agencies that are also our licensees. For example, the closest one would be the hospital, Building 10, down on the NIH campus would have to adhere to our radiation protection standards for all the workers down there -- protection of the patients, and protection of the public that came to visit them.

The Department of Energy would have to adhere to the protection of the workers in all the work that they do and the same thing is true with the military or the different branches of the military, and their workers would also have to adhere to NRC's radiation protection standards.

So without a doubt the Atomic Energy Act, and then the Energy Reorganization Act, did give us quite a good solid stick, if you want to call it, authority for getting done what we need to do.

DR. SHAPIRO: Thank you.

The last question, Alta.

PROF. CHARO: Thank you.

I would like to pursue this cop/counselor observation perhaps now with Ms. Flack because I am going to assume that the NRC actually does play to some extent both roles. They help licensees to understand how to operate safely, will help clarify questions scientific or otherwise, and at the same time we are in a position to impose sanctions at appropriate moments.

We have seen in the human subjects realm people from the investigator community talk about their desire to have a place they could go for advice where they felt they were absolutely no risk of triggering some kind of sanction and I would appreciate your observations about the degree to which this combination of functions within the NRC has functioned well versus having created some problems over the years that have been identified and perhaps some remedies developed.

MS. FLACK: I would like to say that I think it has worked very well. I would like to think that licensees can freely call in and ask questions and make sure that they understand things.

Having spent the last three years working very closely with all the medical specialty boards and trying to respond to their questions and making sure that their input is in the new regulations, I think there is quite a bit of openness right now.

It is not strictly, you know, just the cop and I would like to say that -- to give a specific example. If a licensee is cited for a violation the Office of Enforcement looks very carefully to see if they have identified the violation and if they have taken corrective action before calling the NRC. It is very, very important. It is not just we are out there policing them.

We -- you know, in that case there might not be a monetary fine or it could be a reduced fine or something but we definitely consider all of that when the licensee calls in and has questions about their license. Calls in and says, "Oh, we have done this but on the other hand we have done that to correct it."

So I think it works very, very well.

DR. SHAPIRO: Thank you and I want to thank you both very much for being here today. It is very helpful to us as we look forward to constructing our own sense of what model we ought to use in our area of responsibility.

So thank you very much for coming. We very much appreciate the materials you shared with us.

Just to remind the Commissioners we are going to break now for lunch. We are scheduled to reassemble at 12:45. That is about 65 minutes from now.   That is -- judging by yesterday's time that is about what it takes and so let's break right now and reassemble at a quarter to 1:00.

Thank you.

(Whereupon, at 11:36 a.m., a luncheon break was taken.)

* * * * *

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

DR. SHAPIRO: Colleagues, I would like to begin right away since this is the afternoon of the second day and I know that plane schedules start popping up and people start leaving, and we have some guests here who I am very anxious to hear from.

But, first, as you know, the definition of research -- this is again within our overall project looking at the human subject protection issue in the U.S.

The definition of research is obviously key to this. If it is not research these things do not come in and other issues apply. And so we have told ourselves that we are going to relook at the definition of research to see whether the existing definition is really appropriate given a lot of things.

Given the different disciplines, we all know it was brought up mainly with the biomedicine in mind and not health quality research or health services research, and not with the humanities and social sciences and so on and so forth.

I do not want to repeat all that but we are very fortunate this afternoon to have two people who will speak to us really in the area of health services research, that particular aspect of the issue.

We have Andrew Nelson, who is Executive Director, Health Partners and President of HMO Research Network.

And Mary Durham, Dr. Mary Durham, who is Vice-President for Research of Kaiser Foundation Hospitals.

Both these organizations are, of course, well-known to all of us.

So welcome. I do not know if the two of you have had any prenegotiated way of proceeding on the agenda. I do not know why but it gives Mr. Nelson first and Dr. Durham second but if you have got some other order that you would like to have, feel free.

Welcome and we are very glad to have you here today.

PANEL IV: DEFINITION OF RESEARCH

ANDREW NELSON

EXECUTIVE DIRECTOR, HEALTH PARTNERS AND PRESIDENT HMO RESEARCH NETWORK

MR. NELSON: Thanks for the invitation and I will start out and then hand it over to Mary, and then she will hand it back to me so it will be a continuous presentation.

DR. SHAPIRO: If I could say we think of ourselves as rock stars here, which means we have to talk close to the microphone. It works best.

MR. NELSON: Okay. Just as long as I do not have to sing.

(Laughter.)

DR. SHAPIRO: That is true.

MR. NELSON: The breadth of health services research in the past 25 years has really spread to nontraditional environments.

In an article published in Health Affairs, which I believe you have a copy of, in January 1998, my colleagues and I documented the results of a 1997 survey showing that there were 20 managed care organizations with research groups that accessed nearly 30 million individuals in conducting their research work.

By far, the largest of these research groups are the group and staff model HMO's and the amount of work conducted in them are the largest among the 20.

Staffed with over 150 career researchers and 1,200 FTE's of research support staff, they conduct public domain research that is really dominated by health services research.

Federally funded projects represent more than 50 percent of the $92 million that support their work.

Thirteen of the 20 groups, the 20 research groups, formed a group called the HMO Research Network about five years ago in 1995.

They did so out of good will. It is not an organization with any formal stature with the IRS but one of good will coming together to do collaborations around improving the health of populations that are involved in their health plans and so collaborative working relationships have flourished and we have over a dozen current fairly large projects that are mostly federally funded.

These research groups include locations all across the United States and Kaiser Permanente plans, Henry Ford, Group Health Cooperative, Pugent Sound, Health Partners, Prudential, Harvard Pilgrim and Lovelace.

I want to turn it over to Mary Durham right now who will talk about the nature of the health services research and then I will be back in a few minutes.

DR. SHAPIRO: Thank you very much.

Dr. Durham?

MARY DURHAM, Ph.D.

VICE PRESIDENT FOR RESEARCH

KAISER FOUNDATION HOSPITALS

DR. DURHAM: Thanks very much.

We consider this a great opportunity to talk to this group about a type of research that may be less commonly thought of than men in white coats, men in lab coats. Sometimes we think of it as men in no coats and ties. And that is a kind of research that has been going on and developing for probably the last 25 to 30 years.

And really health services research, which we would like to talk about today, had its beginning in academic organizations under variously titled departments like “medical care organization” or “health systems” or various titles like “medical care.”

And what early academicians were doing and a few health plans were doing was really building a field that now has captured the attention of policy makers and funding agencies, AHRQ, NIH in funding health services research but this is a fairly recent development in terms of the focus of policy makers and funding agencies.

But what I would like to do is begin with a bit of a definition about health services research and tell you that health services research is the study of the structure, function and outcomes of health care

delivery. Especially their organization, financing and quality. And this includes things like patients' access to and satisfaction with care as well as emerging issues like patient safety.

Now these studies vary enormously in their content but what they have in common is they study as system rather than a person or an individual. Patients are not absent from these studies.

In fact, to be able to do these studies we often go to the individuals and see how they flow through these systems, ask questions of them, analyze data about them, but really the focal point of the research is most often the system in which they are located in terms of health care.

So outcomes experienced by these study participants are very much at the heart of these questions that we are asking in health services research.

Let me give you an example. The Rand Health Experiment -- Health Insurance Experiment -- in the 1980's looked at a variety of ways of financing health care, but when it came time to look at the outcomes, things like hospital care, the use of specialists and so forth was the major purpose of that inquiry.

Now these are systematic research studies and

if you think about the definition of research in the Common Rule, these are systematic investigations.

And they are very much involved in looking at questions like, “do interventions that are introduced increase the number of mammograms in a health care delivery system?” Is an intervention likely to reduce the number of teen smokers? Does screening for hemochromatosis have a certain kind of cost quality and outcomes impact on the population? Does a woman who is involved in an intervention become more likely to seek care prior to the birth of her child?

All of those have human subjects but they are primarily about the system itself.

Well, you probably did not expect today to hear about managed care as a topic, but I do want to take a side bar long enough to tell you about why I believe that the issues about research that is happening in organizations like the one Andy and I are a part of, have now come to the fore in thinking about human subject issues and the process of review.

The health care systems that Andy was describing in the HMO Research Network are primarily integrated health care systems funded by capitated financing,and under capitated financing arrangements, providers or health care systems have no incentive to provide treatments that are not effective or medically necessary.

Over use, under use and misuse of treatment all have negative consequences for the organization and for people who seek care in those organizations.

So providing too little care fails to meet the treatment needs of people who come into our health care system.

Unnecessary or ineffective treatments, that is over use or under use, wastes limited resources and pose unacceptable risks to patients.

So with the proliferation of capitated funded models, integrated health care systems, this is much more an issue in looking at programs and whether they work or not than ever before.

In organizations like mine -- my research centers, for example, have been around for 37 years -- these are not new questions, but we have worked under a capitated funding arrangement for the 52 or 53 years that Kaiser has been in existence.

So in the places like Andy described, we are talking about places that have a rich and long history of doing this kind of financing for health care and so it is really there that you find a long history of the sort of work that we will be describing today.

Now health plans that are receiving capitation have come to realize that they must evaluate existing programs, the quality of care, their ability to deliver high quality care, and be very affordable because if they do not do these things they will not exist next year.

So a health plan that cannot deliver quality of care or satisfy its customers or hold the line on costs will disappear from the screen.

So health plans have got to find ways to identify women who are at high risk for breast cancer. They must help people try and stop smoking. And so they -- and they also may be required by employers who sponsor their employees to be our members to meet quality standards set by the National Council on Quality Assurance, so-called NCQA, or other purchasing coalitions.

NCQA does not say how to improve quality. It rather sets certain standards and identifies certain areas in which plans need to have high quality indicators.

And so plans have to experiment on their own in order to determine what works for their members, and under tight financial constraints plans must figure out what works and what does not work.

There are many tools that we use in health care organizations to do these sorts of things. I am going to mention just a few and Andy will mention some more. Patient registries, clinical guidelines, clinical information systems, mail and telephone surveys, all of which are used to collect information and use it in order to improve care.

Plans must carefully monitor patients who have complex medical problems like diabetes, heart disease, depression. The best plans have so-called registries which identify people with diabetes or women who are at high risk for breast cancer and the best health care plans make contact with those individual members even when a woman who is at high risk for breast cancer does not come in for a visit, and without identifying that woman, making contact with her and encouraging her to come in and being proactive about care, the likelihood that all of those individuals who are at very high risk for disease becomes a lot less likely.

So we are involved in active outreach by using things like registries, mail and telephone surveys, and a number of other things that use data, capture data, and also synthesize data as it pertains to our members.

Now health -- and this is the reason I digress to talk about health services research and also capitated financing -- the health plans use the same methods used by health services researchers in order to conduct their business.

For example, plans may evaluate the effectiveness of a postcard reminder system to women who need to come in for mammography and they have a choice in clinic A, for example, to do a study of that sort to see if they can increase screening activity by using those reminders as compared to another clinic where such an intervention might not be used.

A health plan may implement a smoking cessation program in a clinic or with a group of individuals to see if they are getting the bang for their bucks for that effort in order to see if it yields the response from members that they hope.

These are seen as routine management initiatives, but they have to be structured in such a way to answer the question did they work.

It means the sample size must be considered, the design itself has to be rigorous enough to answer the question, and so they look very much like health services research, but they are part of the ever required efforts to improve quality of care.

So these efforts are systematic. That is part of the definition of research. But are these activities research? Unfortunately, my answer to you is that there is no clear line between research and quality improvement and that I do not believe it is possible for us to develop a definition of health services research which would exclude program evaluation in all its forms, quality improvement, population based care, and so forth since they do use identical methods.

However, I do have three things that I would like to offer you as concepts that may be helpful in distinguishing between these, and I must say that most health plans that I know of are trying to use concepts of this sort on a case by case basis to try to decide which is research and which is quality improvement.

The first one is intent. Both research and quality improvement are systematic.   However, their intent is different.   Research is meant to contribute to generalized knowledge. That is part of the Common Rule's definition of research.   And research applies to society at large. It may not apply to the person who is involved in the study, but it is intended to offer something to society at large.

On the other hand, quality improvement is proprietary. The QI activity will launch a program or improve an existing system for the benefit of the population it serves.

Now, interestingly, many health care systems today publish the results of their findings in trade journals. A few of them may be published in main line medical and health services research journals because the world is interested in looking at studies of this sort and they may -- these studies may be rigorous enough to pass that kind of review and be published.

But the major and primary intent of those activities was improving the business and improving the quality of care. I would also like to say, and we will probably get into this later, many of those quality improvement projects are reviewed by IRBs in our delivery systems if the prior intent is to publish and so forth, but we can talk about that later.

The second concept I would like for you to consider is what I call "agent." Quality improvement is done by someone within the organization and it is usually initiated by someone on the quality improvement team. Projects that are initiated by an outside person, even if that outside person or entity is a business partner, kind of like is defined by the HIPAA regulations, that research -- that constitutes research to me. And so the agent of the work is very important.

The third concept I would like for you to consider is the funding source. Plenty of research today is done by employees of organizations that are researchers. The sort of people that Andy was describing. They are employed by health plans. They think of themselves as researchers. They are researchers in an academic sense.

Those researchers compete for funds from the National Institutes of Health, private foundations, to a limited extent pharmaceutical companies and so forth.

Does this mean that their work should automatically be considered quality improvement? Absolutely not. The work is funded by external sources and so those projects are reviewed by IRBs or they follow the Common Rule regulations. And so those sorts of things should be considered as research.

There are some notable exceptions. Some QI projects should be reviewed by IRBs or a comparable body even when they are done for proprietary purposes, even when they are done by someone within the organization's QI team, and even when they are done with internal funding.

These include, in my estimation, things that include anything less than usual care, any nonroutine clinical care, or testing if nonroutine or clinical testing is involved. They should also be reviewed if there is a prior intent to disseminate results outside the ordinary channels of operations reports.

And I think that plans may also need to review projects that pertain to vulnerable populations like HIV, patients with HIV, with mental disorders, children, and a number of other categories.

So let me just end my comments by saying that there are a number of ways that reviews can take place without invoking the Common Rule. Quality Councils review a quality agenda or a quality portfolio for health care organizations. The HIPAAs regulations have mentioned a privacy official, which may also be a person to consider.

But there are many, many unsystematic activities that happen every day in health care organizations that are done to improve care that are really the business -- they are part of the business function of the organization. They are unsystematic and they really do not need review in my estimation.

For example, if a scheduling clerk is trying

to increase the number of mothers who bring their children in for well child check-ups and it is not a systematic activity at all, but something that she is doing or he is doing in his job to increase the number of people who come in, that is not research and it is not a systematic quality improvement activity either.

So there are many examples that fall in the gray zone. Andy is going to talk about a variety of such work and discuss why we believe that we -- while we strongly support the IRB, we review many more things than are required to be reviewed by the IRB, all of our privately funded activities, for example, go to the IRB although they are not required to do so, but we also want to avoid promulgating rules that have a chilling effect on the day-to-day quality improvement activities that are absolutely necessary for us to do our business.

So I will turn it over to Andy.

MR. NELSON: Thank you.

I wanted to let you know that both Mary and I are institutional officials within our own organizations and so we have our own IRBs to manage, so we are speaking from experience as well, as Mary has a connection to the rest of the Kaiser research organizations. So this is reality for us and the

discussion that we have today here with you comes from experience, not only from our own groups, but also the HMO Research Network as we have had group discussions about these issues.

Each of these research organizations that we have talked about have IRBs. They follow the federal regulations in using their good judgment.

They have a special relationship that other IRBs in academic institutions may not have in that they are connected to a population and so often times in our organization, for instance, our Board of Directors are made up of members and patients. Do you think that they want to know what our IRB is looking at in terms of research we are engaging in? You bet they do.

And so the scrutiny that we use within our IRB actually, I think, goes beyond many of the standards that are talked about in the federal regulations.

The context of this work in a health plan population have two special challenges that I think we are facing that I wanted to elaborate on today.

The first is the increasing state and federal regulations that we see coming at us. The second is the adequacy of the Common Rule definition and the application of regulations in reviewing health services research.

In Minnesota there is a data privacy law that dates back to the early 1970's that had its origins in Sweden from the 1940's. And in 1996 there was an amendment to that state law that looked at requiring patient consent to access any individual identifiable information for any research purposes.

And the chilling effect that Mary talked about did go far beyond managed care organizations, but went to academic institutions with a fear that this might damage epidemiological studies and long-term longitudinal studies that look at cohorts over a period of decades.

Other states have recently passed or are considering legislation like this to regulate the access to private medical information and the accountability for monitoring that access.

An increasing burden is being placed on IRBs when we take these rules on that end on researchers to be (1) informed so they even know that the laws exist; second, do they understand them and the implications; third, how do they make informed decisions when they are relating to those in order to comply to the -- both complexity of the existing but the new rules that are being asked.

And I think IRBs are doing a very good job of that. They often spend more time reviewing the health services research studies because of these complexities than they do the biomedical studies that may actually have more physically harmful risks involved.

I think that requiring the traditionally strong emphasis on what we require as part of our IRB biomedical research backgrounds, and there is an increasing diverse expectation that we are able to handle health services research, and so in one IRB the breadth of skills and the diversity of expertise has to be there that will bridge across those biomedical studies to health services research to population type studies that involve public health agencies as well.

These research groups that we talked about typically require researchers to obtain a certain level of understanding of all of the research subject protection policies and so some of these groups actually require certification and educational process like many academic institutions do.

And many of the investigators are also asked to be on the IRB because they are the wellspring of knowledge about that area and so it promotes knowledge back into the research community at the same time.

There are some common concerns, though, when an IRB has to take on a study that goes beyond their own state and so in this research network we have studies that go between sites, that go between sites in academic institutions, that go between sites, academic institutions and public health agencies both at a national and state level.

And so looking at all the rules that might be considered in that process you can imagine the evolving study designs and methodologies that have to be considered when you are thinking about data privacy and some of the regulations, and it can be very confusing in order to have a single IRB understand each state's regulation that might be involved in a multistate study that their organization is hosting.

With this background I would like to really have you understand that the burden on IRBs are increasing and our IRBs are made up of volunteers. The volunteer nature of IRBs in the fulfilling -- I do not know if many of you have been on IRBs yourselves but there is a fulfilling role that you have individually and the weight of that, the decisions, and the sort of pride that comes away from individuals participating in that is really a national treasure,

and the threat that we have with the complexity that we are throwing at our IRBs is that it might be wearing them down a little bit and so I would have a concern over that and challenge us as administrators, as policy makers, to make sure that we state our policies simply, that we do so clearly, and give them guidance to make decisions without burning them out.

Turning to the adequacy of the Common Rule definition and the application of regulations when reviewing health services research: the Common Rule definition of systematic investigation by itself is a defining factor.

Often, as Mary said, our health care organizations are involved with quality initiatives using the research methodology that is no different, with no intent to disseminate. However, I want to reiterate the exceptions when we are looking at health services research studies, that if there is prior consent there needs to be review.

If there is less than adequate or less than usual care, not adequate care, less than usual care it should be reviewed, and the nonroutine care or testing should be reviewed, and consideration about vulnerable populations.

If we had in addition to the common reviews

of what we define as research under the Common Rule, if we added all of the quality assurance activities within a health plan to the IRB's schedule, they would melt down. There is not enough time to do that and we should all be happy that there are health improvement initiatives within health care organizations and look at different mechanisms to apply policies there.

Some of the application of regulations to consider when we are looking at examples, the electronic encryption issues with electronic data. Oftentimes our IRBs are struggling to make sure that each study with the amount of collaborations and electronic data HIPAA is addressing as well, but each IRB has the responsibility to look at an individual study to ensure that that privacy and that data is going to be held confidential.

The types of studies that can cause extended review by an IRB often are the registries, the surveys, and the types of studies that are noninterventional but involve vulnerable populations. And our IRBs can spend extended times talking about all of the different harms which come from disclosure that are not necessarily physical harms.

Finally, I think that the definition of the -- in the Common Rule is ambiguous and the regulations between the agencies differ but IRBs understand this intent from our experience and they are able to make firm and informed judgments.

But I think what would be helpful as we get into this more complex age of regulations is that we need some balance here. We have organizations that have oversight, strong enforcement and compliance monitoring, and consequences for organizations that do not look at the regulations seriously.

But what we do not have is a balance of case studies, supportive education, training materials that would provide guidance for our IRBs and researchers. I think that is necessary if we are going to look at true compliance and a positive and proactive future with research and the protection of human subjects.

Thank you.

DR. SHAPIRO: Thank you.

Thank you both very much.

Let's go to questions from members of the Commission.

Alex?

DISCUSSION WITH COMMISSIONERS

PROF. CAPRON: Has the HMO Research Network developed such guidance as to the definitions of research because your article uses the word "research" to -- as far as I can tell -- encompass some of the things that Mary was describing as quality improvement activities and in your closing remarks you just described the need for a definition. I wonder if you had in the private sector agreed among your HMO colleagues in the Research Network on such a definition.

MR. NELSON: Each of the 13 organizations has its own, and we have collectively in an annual meeting starting two years ago began discussing that but we have not come to a place. We have not debated it or had the intent to come to that place yet.

PROF. CAPRON: When you say that IRB review is needed when you go beyond certain aspects of quality improvement and the ones that I noted were when you have a reduced level of care, when you have nonroutine testing, and you suggested maybe -- I was not clear about this -- whether there is an extended survey or a registry that you would expect an IRB to have looked at the work.

I was not clear whether again there was a sense of greater risk involved in activities or it was not just that they were going to be producing more knowledge as far as I could tell.   That was not -- I mean, the generalizable knowledge was not the thing.

What is it about those activities that led you to say that these would be categories where you would expect IRB review?

MR. NELSON: I think Mary -- I would like to ask Mary to help me with this but first from the experiences at Health Partners when we produce a registry for research purposes it can be combined with health improvement purposes like an immunization registry, and to discover how we can work with different populations that may not have a high enough immunization rate so that we can improve that, and we use research techniques to do that.

The accessibility of that information concerns the IRB as we are getting into it, and so to ensure privacy issues are upheld and regulations around access to that information are not easy to debate, and so there is some guidance that we have from existing registry information nationally, but each case is so different.

DR. DURHAM: I would say that the reason that registries have gotten attention from the IRB is that they are very expensive to put together and that they often are a result of researchers getting external funding to get them established.

Then once they are -- and that would trigger the IRB for us. We would always do that.

And then in addition the way in which they are used would be by a mixture of -- the products of those registries would be a mixture of things. One, quality improvement where it truly is -- it does not -- it is not used beyond the proprietary interests or the self -- building -- improving the business part but there also may be papers that are written using that data, and so those always go to the IRB.

So it is kind of a branching point if you will. The IRB -- the registry itself gets constructed with external funds so it is reviewed and then there may be a different use of it, one reviewed and the other not reviewed, depending upon its intent.

PROF. CAPRON: Is there any other common theme that you would see in such a determination besides outside funding or possibility of publication where you are going to want a journal editor to be able to say, "Yes, I can publish this because you went through the usual IRB process." Any other common theme to why you would consider something IRB-related research rather than another quality improvement activity which you say you will go ahead without the IRB?

DR. DURHAM: Well, those three things that I

mentioned. The intent, the agent and the funding are kind of the umbrella concepts that I think encompass most things. Teaching activities are often exempted from IRB review because --

PROF. CAPRON: Well, on the intent what I did not understand was the intent, as I understood it, you said research is the intent to produce generalizable knowledge, quality improvement was the other category, that is usually proprietary, you said. It is the desire to do something that will help the organization perform better.

But later on what I understood Mr. Nelson to be saying was when you look at the quality improvement activities, things that are intended to help you behave better, sometimes some of those are regarded as appropriate for IRB review.

DR. DURHAM: Yes.

PROF. CAPRON: So maybe I am really quoting him and not you at this point to know how --

DR. DURHAM: Well, those categories, the three concepts that I mentioned to you are not mutually exclusive. Any one of those would trigger a referral to the IRB, for example. So I think that is the answer.

DR. SHAPIRO: I would like to pursue this

point just a little bit to help my own understanding.

If you think of why there is a definition of research altogether, at least in my mind it is in part to try to identify those characteristics where conflicts may exist or those projects where conflicts might exist, that is you would not have simply the patient's interest as a doctor in mind, but other interests in mind, and so you try to develop a situation where there is a conflict there, and say, well, where there is a conflict, there is a need for some regulation, and research is a part of the answer to that, defining research -- distinguishing research from clinical activities.

In this case, as I listen to you speak if it were true, of course, that overuse, underuse and misuse were always strong disincentives, then it would be hard to find conflicts between what you are doing in quality improvement or what you are doing to manage the organization and the care given to the patients, care responsibility to patients.

And I do not want to discuss whether that is always the case or not. I have my own view of that. This is not the time for that discussion.

But do you think that perhaps looking at it not by, as Alex and you were just talking about, intent, agent, funding source, systematic/nonsystematic, those are all useful and I think maybe they are the correct ones, but what about just focusing attention on where conflicts exist where you have something other than the immediate health needs of the patient in mind or potential conflicts? That is right. Conflicts or potential conflicts. Is that useful or is that not useful?

DR. DURHAM: Well, I think -- it is hard to -- I do not know exactly where you are going with that. I think that the thing that I fall back to in that distinction -- we are always trying -- every -- all of the research would also fall -- I think what I am hearing you say is all of the research that we do would certainly fall under the improvement of care.

DR. SHAPIRO: Right.

DR. DURHAM: I mean, we would not be doing it. All of it is intended to improve on that misuse, underuse and overuse criteria.

But the research activities are not intended -- not necessarily intended for the benefit of patients today and so --

DR. SHAPIRO: Right.

DR. DURHAM: -- therefore, if such a thing happened it would require for us to ask people if that was okay and get their consent in order to be involved in it. If it is for the direct benefit that is where the conflict comes in because it becomes harder to distinguish between what is -- what we ought to be doing anyway.

The thing that presents wonderful conflicts for us is the fact that external funding agencies, people outside of our organizations, know that we can generate new knowledge within it and so, therefore -- and very appropriately -- federal regulations that have to do with research come our way.

If we lived in a world where there was not an external funding source, I feel like we would need to do this work anyway, and, in fact, there has not been a lot of funding for health services research until recent years.

My research organization is 37 years old and so we were patching it together over all those years, often with external funding. But even if we did not have internal funding the conflict comes from the fact that we need to do it some way some how.

DR. SHAPIRO: Thank you.

Bernie?

DR. LO: I want to thank both of you for a very clear and well organized presentation. It strikes me as I listen to you that your organizations in your network have real commitment to making sure that projects that might pose ethical concerns or risks for patients are reviewed by someone other than the researcher, usually an IRB-type mechanism.

I have two questions to follow-up on that.

One, as I look at the list of people that responded to your survey, they are pretty much the established HMOs. Many are nonprofit. Many are staff model.

What do we know about the -- the first question is -- what do we know about the willingness of the aggressive for profit organizations that do many of the same types of work, that may involve less than usual care and the other criteria that Dr. Durham mentioned? What do we know about the scrutiny that they put those projects under?

Is it similar to what your organizations do?

And secondly is the resource question. And both of you very rightly pointed out the economics of health care and the era where costs seem to be rising again and employers do not want to raise premiums too much, what sort of institutional support do you give to your IRB that does so much work?

You spoke, for instance, of volunteers. Are clinicians who are on your committee given time off or do they do it after hours? What kind of staffing? What kind of budget do you allocate?

MR. NELSON: I will take the first question.

On the survey when we went out -- and this was not a thorough survey of every managed care organization in the country -- rather it was a search of the literature.

It was a knowledge base of people who had engaged in research and the people that they knew engaged in research. We found 50 organizations that claimed to be doing research.

DR. LO: I may not have made my question clear.

MR. NELSON: Okay.

DR. LO: It was not the research, but it was the things that use health service research techniques for quality improvement areas, but which do it in ways that both you and Dr. Durham suggested ought to undergo the same kind of scrutiny and, in fact, do within your organizations.

Is similar scrutiny put in place in other people that do not publish the research and, therefore, were not included in the surveys you did?

MR. NELSON: There may be single investigators out there in those organizations. From my knowledge and our background in this work, we are not familiar with any organization out there beyond this group of 20 that actually claimed to be doing public health research.

DR. LO: All right. It is not that they are doing research. They are doing QI that meets your other --

MR. NELSON: QI, yes.

DR. LO: -- criteria.

MR. NELSON: I understand.

DR. LO: Your organizational --

MR. NELSON: Yes. And the oversight of that -- there is an absence of knowledge. I do not know of -- no. Do you know?

DR. DURHAM: No, I do not know.

The second part about the IRB support, I can address that. It is all over the board in terms of how organizations like our's -- once again, I do not know about organizations unlike our's. But our's are supported by the research enterprise -- by the organization, the parent, the host organization.

And, also, because IRB is an essential

function of doing research when dollars come in for research projects, indirect dollars are generated which are then used to support the IRB but the models themselves vary.

For example, IRB -- the Common Rule is very clear about who -- that people need to sit on -- the physicians, people with knowledge about research and so forth, most of it -- I will make a bold statement here that most of it is really volunteer work.

Sometimes honoraria are given to people but it -- given the number of hours they work in a single year on this it is a very small matter.

Physicians are very often given release time to participate on IRBs. We use retired physicians -- and this is probably a good comment.

Many of our retired physicians love to come and sit on our IRB because they have time to devote to this activity whereas people who are practicing have far greater difficult getting time away from their clinical schedules to participate. So we have had wonderful experiences with recently retired physicians who give a huge number of hours.

MR. NELSON: Our experiences that we have had long-term members both from the physician staff and from the community, but we need to pay our chair and vice chair because they really have to spend a good chunk of time reviewing all studies.

DR. SHAPIRO: Thank you. We have three people. I will ask again given the time to keep questions and responses as brief as possible.

Tom, and then Jim, and then Larry.

DR. MURRAY: Hi. What you did today was both encouraging and somewhat discouraging.

The encouraging part was it is good to know that there are leaders of the field such as yourselves who are so thoughtful about this and I think trying to do the right thing.

It is discouraging for those of us who are trying to figure out how to operationalize a definition of research that would be applicable, readily understandable, and most importantly capture what is morally significant to the public about what is special about research and the protections that we should accord subjects.

Mary, you gave us three. Funding source, agent and intent. I am going backwards because intent is the most promising but I think even that in some sense fails.

Funding source could come internally or externally or out of your own pocket, but it could still count as research. That is true in university settings. It is true in HMOs.

Agent: You could hire an outside Beltway bandit or consulting firm to come in and do a QI study that was not at all generalizable.   I mean, I am not sure that the agent is going to work.

Intent is the one that is hopeful, but even that is a problem because -- I think, Mary, you told us that sometimes you do a QI study really intending it to be a QI study but it is really interesting and you want to publish it. Was it research? Not in the initial intent but in its -- ending up being used as generalizable knowledge, yes.

One little wrinkle might be what if all journal editors -- what if all journals and editors agreed that they would not publish any study using human beings, whatever its announced initial intent was, if it did not go through appropriate IRB review even if it would -- and whatever. I do not know if I am being very clear here.

In other words, if I did a QI study and it did not go through the IRB, loved my results, wanted to publish them but I could not get them published, it would no longer -- it would not be generalizable knowledge. I mean, that is just a little possible wrinkle.

DR. DURHAM: One of the problems with that -- I mean, it is good to be -- we want to be able to transport knowledge from one place to another. We want to be able to do quality improvement.

One of the -- a couple of things that concern, I think, most of us who have been talking about this within organizations is that we do not want people to be so daunted by the review process that they will stop doing the work and this could very well happen. They could say it is not worth the IRB-style review.

And that is why at least within my organization, the HIPAA rules that were just published by the Secretary in calling for a privacy officer, that we do not object to something of that sort if we can use the judgment of that kind of person or a quality council or some other entity.

The second point I want to make here is that there is grave concern on the part of IRBs that it is going to be even more confusing to pile quality improvement projects that are meant for the -- you know, for the use of the organization into the review list, not only due to volume -- and I agree it could cripple the IRBs ability to do its work but also --

and also drive off the people who have very kindly volunteered for this work but now the work would be threefold and fivefold beyond what it is currently doing.

So I am quite serious. People love to do work that is quality improvement, in organizations I have found, but there is just so much that they will do to -- you know, do paperwork and get reviews done that they might not choose to do and so there is a balancing act here.

DR. SHAPIRO: Thank you.

Jim?

DR. CHILDRESS: Thank you. Your presentation and the discussion that has followed have been very helpful, I think, in showing us some of the dangers and pitfalls that we face in trying to sort out this whole area.

Two quick questions. One is in the health plans that you are familiar with, is there any kind of disclosure up front about quality improvement activities whether they are called research or not?

That is the first question, and even though such a general consent might not be adequate from say an ethical standpoint, still it would be useful to know if that is present in the health plans.

And then second in the discussion of privacy and confidentiality that was fairly brief in your comments and focused mainly, Mr. Nelson, more on the problems of the state laws that might impose a lot of restrictions in this area, but what kinds of concerns have been expressed within both quality improvement work and research that goes on about privacy and confidentiality within the organization?

So two parts of the question.

DR. DURHAM: Do you want to take the first one and I will take the second one? The notice part.

MR. NELSON: Yes. There is a common notice that is in a health plan contract with a member that I am aware of, at least in our two organizations, that when a member joins they are notified that we do conduct research and that we do use records.

We will ask them if they are involved in any study at all individually that we will ask them about that study through a consenting process. So we do have those disclosures and there are notices up front but it is not adequate in terms of individual study involvement.

DR. DURHAM: And other organizations that I have been associated with have had “Patient Bill of

Rights” kinds of things for consumers, and in it one of the points will be that we do research, but it is not something that is on -- posted on every medical office wall, although we are usually recruiting for studies and there is some kind of notice on virtually every clinic's board about that.

The second question about confidentiality --

DR. SHAPIRO: Go ahead. Do you want to press your button, Jim?

DR. CHILDRESS: Sorry. Thank you.

Okay. The notice up front about research. So the question is when you are talking about IRB review, are you also assuming then that you will want consent on the part of people who are participating in it, because your movement to the IRB is again not constrained by the requirements of the Common Rule, as you were talking about, but your felt need to get some additional input into the evaluation of the protocol?

So I guess I am not quite clear. This consent up front to research would be different from consent up front, and I am using the term "consent" loosely here knowing all sorts of constraints for the people to really have a choice and so forth.

Is that -- are you -- when you were talking about this notice and you used the term "research," both of you used it, were you including under that quality improvement? I mean, was that at this point a very broad category, not a specific category?

MR. NELSON: If it meets the definition.

DR. DURHAM: Well, the information would be conveyed both that we do quality improvement and research and then when it is research or some of that quality improvement the IRB, of course, requires that we get informed consent and we do so. So it is a multilayered process.

DR. SHAPIRO: Thank you.

Larry?

Jim, I am sorry.

DR. CHILDRESS: If they could deal with the privacy and confidentiality question.

DR. SHAPIRO: I am sorry. I apologize.

DR. DURHAM: We are very concerned about making sure that quality -- that confidentiality and privacy are very strongly inculcated into our world. I will tell you why. This sounds like apple pie and motherhood, but it is really true.

Unlike a university, where you might put out a newspaper ad to recruit subjects for research, people are members and so we are very careful not to approach them and ask would they like to be

participants in studies so frequently that it is burdensome or that we -- and that we maintain this research relationship with them.

And so we want to make sure that we have standards for research that go beyond what the federal requirements require because of that relationship with them.

And so I think that we have taken steps far in advance of other researchers because we have to nurture that continuing relationship with people so we are very concerned and we want to be there and beyond in each of these instances.

MR. NELSON: Two examples of that. One is that not just for federally funded research but we review all research with the same standard.

Second that most -- in Mary's case all of the health services research studies which would be required to go through only an expedited process are going through a full review process.

DR. SHAPIRO: All right, Jim?

DR. CHILDRESS: Yes.

DR. SHAPIRO: Larry?

DR. MIIKE: It seems that what you are trying to do is responding to the universe that IRBs look at, which is research activities.

But if you forget for a minute that boundary of research and trying to be flexible around how you compare quality assurance studies versus research, it seems to me that the major concerns that would be raised would be conflict, consent, safety, privacy and confidentiality.

So that if we could redesign a system that focuses more on the risks inherent in any system rather than on the definition of research and if you could balance it off so that you do not end up with an IRB that has gotten more things added on to it, would it make sense to have a review regardless of whether -- especially in the kind of organizations you have, which is not concerned so much about whether it is a research project or quality assurance, but whether looking at these issues of -- and in your case most of your studies do not really deal with safety in classical physical safety issues -- so you are basically dealing with conflict, consent, privacy and confidentiality.

Would that simplify your system for you?

DR. DURHAM: I am presuming that -- I am trying to imagine what it would look like. It would be minimum risk or minimum necessary -- minimum. Just thinking of minimum risk as the concept and then all comers would be reviewed if it was more than minimal risk. Could I make that assumption?

DR. MIIKE: Except that I am not sure if privacy and confidentiality would be considered minimal risk.

DR. DURHAM: Right.

DR. MIIKE: Am I right?

DR. DURHAM: It might. It would certainly be a useful tool for us. Right now we are kind of overlaying that and, in fact, that whole concept of minimal -- I am using the term "minimal risk" as really the reason that we bring more into the IRB than we are required to because we are saying we want to take a very narrow view or very broad view really of what might conceivably constitute risk.

I do not think I have answered your question.

MR. NELSON: For a research organization to monitor a whole health care organization and the quality improvements and the medical staff and all the clinics would be impossible and so we really have to look to the greater organization to have this privacy officer function, a compliance officer and the regulatory compliance process.

So there really needs to be a much greater responsibility there than just a research organization.

DR. MIIKE: But it seems to me that if you have one body that focuses on the issues I mentioned, conflict, consent, privacy and confidentiality basically in your organization, you soon develop an institutional memory within a given body rather than having --

MR. NELSON: This is true.

DR. MIIKE: -- I mean, you heard -- if you were here earlier you heard what is happening in all these different areas where you have privacy laws, you have the IRB system.

MR. NELSON: Yes.

DR. MIIKE: You know, all of those kinds of things and it is so scattered that no one really has a grasp on it and it seems that -- I am just asking whether that might not seem a reasonable alternative if we can get around the issue about what is a research project.

DR. DURHAM: I think so. I mean, it would be a more -- it would be a way to pull it all together and it would have to recraft to the IRB system because it is too big and it is too much for the people who currently -- and it might also be a different set of rules that are applied once you got -- once you have

gathered those projects together.

You might need to look at research which is not going to contribute to the care of that individual right now, which we are calling research, and the Common Rule calls research, versus something that is quite different.

It takes a different level of skill perhaps to scrutinize those two different things even if you pulled them together in one place.

DR. SHAPIRO: Thank you.

The last question will be from Rhetaugh.

Rhetaugh?

DR. DUMAS: I just wanted to make an observation because I had some real question about where to draw the line between what you are calling research and what you are calling everything else. I think that is where the critical issue is.

There are issues of safety and risks involved in the enterprise's business to people and that there is a temptation to ask what you are doing about that but that is not our primary concern.

We are concerned with research risks and so the definition of research for me becomes a very critical issue and I have a hard time distinguishing between -- even with your criteria -- between what you

are calling research and what you are calling quality improvement.

I gather that that is something that you probably continue to struggle with.

DR. DURHAM: Right.

If we -- if we cannot -- if the people responsible for research like Andy, and I cannot decide and if we are face to face with a quality improvement person in our organization, and I think it is research and that person thinks it is quality improvement, it has to be adjudicated by, let's say the medical director, and he or she has to make a call based some organizational memory and some decision rules that we have developed.

So I know that all the organizations in the HMO Research Network have been hammering away to help that medical director, who is going to adjudicate this, how to make that call, but it comes to -- a lot -- most -- many of them fall easily into one camp or another but there is a number in the gray zone and those decisions are made on a case by case basis.

I am saying I simply do not know how to do it other than looking at those case by case distinctions.

DR. DUMAS: Right. One more comment, though.

I have a great deal of difficulty with the criteria of intent because a person may not intend that they are doing research and yet all of the other mechanisms in the process would fit the criteria for research in my definition.

DR. SHAPIRO: Well, thank you.

First of all, I have -- well, thank you.

And I was going to make a gratuitous comment at the end.

I want to thank you first because that is the more important part. You really have brought out for us some of the really key issues that we are interested in and I very much appreciate your efforts and your willingness to come down here and speak to us.

I have admired over time a great deal of the research that has come out of organizations such as your's, and have read it and am grateful to you and your colleagues for having produced it.

Now comes the gratuitous comment as an economist. That is why this sort of does not count. You can consider this meeting almost adjourned.

If it were true, as I said before, the overuse, underuse, and misuse were the driving incentives for these organizations, no expense would be spared for IRBs if you needed it. It is just not a -- we hear this all the time from everybody who does research and it just seems to me that is a disconnect.

That is a gratuitous comment and it does not need any response but it is something you might think about as you think about it.

Well, let's be -- I understand that our next panelists are not yet here. Is that still correct?

In that case let's take a 10 minute break and try to reassemble at five after.

(Whereupon, at 1:53 p.m. a break was taken.)

DR. SHAPIRO: I would like to get our meeting underway again.

Our next and final panel today is an attempt to bring Commissioners up-to-date on some important initiatives in Congress and very fortunately we have two important staff people out here spending some time with us today.

It is Paul Kim and Souheila Al-Jadda.

One is -- of course, Paul, as you know, is with Congressman Waxman's office.

And Souheila is with Congressman Kucinich, as you all know, from the House of Representatives.

Paul, I think you are going first.

Welcome.

Thank you very much for taking time to be with us today.

PANEL V: UPDATE ON CONGRESSIONAL INITIATIVES

PAUL T. KIM, J.D., M.P.P., COUNSEL

CONGRESSMAN HENRY A. WAXMAN,

UNITED STATES HOUSE OF REPRESENTATIVES

MR. KIM: Thank you very much, Dr. Shapiro.

Can everybody hear me?

DR. SHAPIRO: It actually works a little better if you use the one on your right and just pull it towards you a little bit and push the button. It will turn -- a red light will go on.

MR. KIM: Great. Is that better?

DR. SHAPIRO: That is better. Thank you.

MR. KIM: Great.

DR. SHAPIRO: We think, as I said before, we think of ourselves as rock stars. You have to stay close to the microphone.

(Laughter.)

MR. KIM: Thank you very much for the invitation to appear on behalf of my employer, Congressman Henry Waxman.

We are delighted that the Commission is meeting on a regular basis and is conducting its evaluation of human subject protections in the United States.

As a matter of historical interest, Mr. Waxman has always been a very strong supporter of the previous work of previous national presidential Commissions, and our hope is that in the near future we might actually encourage congressional interest in authorizing on a permanent basis a Commission of this kind to avoid the kind of pendulum of interest that has swung back and forth as different Commissions have been authorized and then fallen out of activity only to find a period of inactivity at a period of importance where bioethical issues are not being scrutinized on a national level.

So this is a -- just to begin, that is an issue of great interest to our office and we believe to other offices as well on the Hill.

One of the reasons we are very, very encouraged by the Commission's activities in human subjects protections broadly is I think congressional interest is at a high at the moment -- certainly in the past few years. And it is in no small part because of the previous work products that the Commission has generated, the reports on stem cells and on cloning, for example.

The enforcement actions by OPRR recently have also been a trigger for congressional interest. The disclosures in the media about clinical research practices, including patient recruitment.

Those have also been a spur to congressional scrutiny but to date it has not manifested in formal hearings or compulsory hearings, but our hope is that with the completion of the Commission's report on human subject protections that might well be the basis for formal congressional action on this topic.

One of the issues that our office has taken a great interest in of late has been in the field of gene therapy research. It is a subject that I know you discussed extensively in this morning's session, and I will not repeat or go over territory you have already gone over but we find it notable that on the 25th anniversary of Asilomar we find ourselves addressing very much the same questions that were tackled then, by many of the same participants in the debate, which is also of note to us.

But we think that some of the failures in oversight, institutional oversight and in regulatory oversight in gene therapy research are notable because they have great relevance to human subject protections elsewhere in other fields of research.

From what we understand from data given to us by the NIH and FDA and from the media accounts of some of the problems with gene therapy research there have been clear failings on the part of principal investigators and on the part of IRBs and different institutions in adhering not only to the NIH Guidelines but also to 45CFR46.

We have noted with great interest that the private sponsors of much of this research have to date taken a very legalistic approach to their obligations under current regulations, insofar as they have claimed that responsibilities for adhering to the NIH Guidelines, at least, stop at the institutional door and that the private sponsors, in having a legal obligation to comply with the guidelines, had no responsibility as far as due diligence was concerned to ensure that the investigators that were sponsoring were also complying. We see that as -- if not a loophole, then certainly a future topic for scrutiny and oversight.

Finally, there have been well-documented problems in regulatory oversight by the FDA and NIH. You have probably seen all the materials that have gone back and forth between Congress and the agencies.

You have undoubtedly seen or reviewed the transcript for the subcommittee hearing on the Senate side, but we think most notable as far as FDA's actions were concerned was their failure to communicate in a timely manner with the RAC and with the NIH regarding compliance with the NIH Guidelines when they had such a substantial body of information and when they were serving as *ex officio* members.

That kind of failure, I think, is extremely disturbing to us. We can only hope that it is truly unique and does not reflect upon the FDA's oversight of clinical research through the IND process.

And as far as the NIH is concerned, we do understand that you have heard about the prospective changes that the Administration will take on in the next few weeks to, hopefully, remedy these problems, but it was the truly unprecedented failure in adverse event reporting, the scope and the variety of noncompliance, which we have documented, which was truly surprising to us and we hope will be remedied very, very shortly.

But that kind of failure again we felt went to at least, in part, a change or a perception of conflict of culture in the NIH between its funding mandate and its responsibilities to oversee this

research.

That was made clear to us directly by the agency in their communications and so it is not as if it is a question in doubt. It is something that they recognize as being something that needs to be worked on.

As far as the public attention that has been paid to gene therapy, there has only been one documented death attributable to an experimental therapy and we are very well aware of the potential to over react, to overstep as far as Congressional action is concerned, but we would hope that we could take this opportunity and that the Commission will use this as an opportunity to hammer on the fundamental importance of compliance with human subject protections, that the NIH Guidelines are only one manifestation of those kinds of protections, and that we should use this as a good opportunity as a stepping stone to reforms and to enacting meaningful changes that will assure that there is a zero tolerance culturally, as well as in practice in the field, and that the agencies do take their oversight responsibilities as seriously as possible.

I want to make a quick comment about what our office is working on currently. Although there have

been no hearings in this past session of Congress on human subject protections, we are working on legislation.

And the reason we are is not because we intend to overstep or anticipate what the Commission is doing or what Congress might do by ways of oversight hearings, but because we believe that many of the problems with human subject protections are well documented.

There are the GAO reports, the Inspector General's report, and of course the Advisory Commission on Human Radiation Experiments. We noted their findings with great interest as well several years ago.

If it is at all helpful to you I could walk very quickly through some of the problems we perceive and need to be addressed and welcome the opportunity to hear from you through your questions, as well as areas where you think our attention should be directed.

But, in brief, the first and foremost problem obviously is the application and scope of the Common Rule protections and of the additional subparts under 45CFR46, the vulnerable population protections.

We cannot see any argument in equity or

principle why there are some subjects of human research who are not protected by these standards and there are others who are. And that that disjunction is simply a function of funding source that to us does not make any sense, and we would welcome any argument from any parties on -- in the field or from other stakeholders, as to why that is an appropriate distinction but we believe that is one that should not stand and should be remedied quickly.

We have in our discussions with stakeholders heard about the potential burdens of extending the Common Rule and the vulnerable population protections, but we have not seen any reasonable calculation of what that burden would be or what the additional resource constraints would be on institutions and whether that would be overly burdensome.

Again, taking -- bearing in mind that there is a powerful argument in equity for extending the protections, and we believe that any additional costs would be justified by those arguments.

We are concerned about and took note of the report, the Commission's report on individuals with -- and I hope this is the appropriate term -- impaired decisionmaking capacity.

We noted that there are -- there is a need to

revisit the additional protections under the -- not the Common Rule, but the other subparts, and we are looking particularly at the protections as they apply to children, given the implementation by the FDA of incentives for additional pediatric research and their own regulation in that regard. We think that is an area that should be examined in great detail.

We are very concerned about the deficit of information regarding informed -- regarding IRBs and the extent to which the institutions are complying with the NIH Guidelines and with the Common Rule. We do not know how many IRBs there are, what standards they adhere to in terms of education or the adequacy of training for their members.

We are certainly concerned in trying to obtain some sense of the number of subjects who are involved in the research and what categories of research they are involved with.

We are very cognizant of the work loads that the IRBs have currently and the need perhaps for additional resources, whether they be institutional or federal resources, to insure that they are doing their job appropriately.

We have seen the literature on informed consent and took note of the NCI's recent actions to streamline or make their informed consent forms more understandable.

The whole notion that the informed consent process should be truly informed. We are willing to be educated about some of the deficits in that process and hope that the Commission's report can contribute to our better understanding of what needs to be done to make informed consent work more appropriately.

We are interested in the questions of disclosures to patients, not only the conventional categories of information that are disclosed to them through informed consent, but what are things such as financial conflicts of interest. Investigator conflicts are appropriate categories of research -- of information to be shared with the patients, in what contexts and what kind of information would be truly useful to them in making informed decisions.

And finally we have applauded the movement of OPRR to the Office of the Secretary. We believe that will help them carry out their job in a more effective and efficient manner but we are very interested in seeing whether the resources available to OPRR are adequate, whether there are other forms of sanctions that might be appropriate short of the withdrawal of a multiple project assurance for institution.

We have heard criticism of OPRR on that score, but to be frank, we are not sure what one can do as a federal regulator when there is widespread noncompliance at an institution. We would welcome your scrutiny of that question and see if there are any contributions or suggestions you might have as to what might be other sanctions that could be used in this area.

The legislation we are working on currently is with Congresswoman Diana DeGette, and our hope is that there will be bipartisan and bicameral interest in sponsoring it. We have already seen -- had expressions of interest from the Senate as well as the House and from both parties. Obviously this is not a partisan issue and it is our hope that that will be true when we introduce the legislation.

And finally let me just emphasize again that we are looking for with great, great interest the findings and the recommendations that the Commission will have. It is something that we intend to carry forward with and, if at all possible, we might hold the introduction of the legislation in abeyance until we have had an opportunity to review and incorporate your suggestions into any legislation.

Thank you.

DR. SHAPIRO: Well, thank you very much. I appreciate it.

We will hold questions for the moment.

I just want to make a few comments in response to some of the things that you have said.

We certainly would like to participate in any way that is helpful with initiatives on the Hill that we can contribute to and we are very anxious to contribute to something that will deal with problems, which I think we know are out there that need to be dealt with.

We are very grateful, of course, for not only Congressman Waxman, but a bipartisan group of people have been very supportive of initiatives in this area over time, of which Congressman Waxman is certainly one.

I do want to say just for point of information, is regarding the scope of the Common Rule, that NBAC has been on record for the last three years since 1997 saying that we believe that is a problem and so we certainly share your view of that and I think we increasingly share your view regarding the deficit information regarding whether IRBs, institutions, investigators and so on are meeting their responsibilities under current rules and regulations, let alone those that might come up.

And we are certainly focusing on that as well as on the last item you mentioned, that is OPRR, which has gone through one transformation now, and the question is whether that is the right one and so on.

Those are all issues which we share and I was really very interested to hear your own perspectives on that and very grateful for that.

If you do not mind, we will just go on and hear from your colleague and then we will see what other questions there are.

Ms. Souheila?

SOUHEILA AL-JADDA
LEGISLATIVE AIDE
CONGRESSMAN DENNIS J. KUCINICH
UNITED STATES HOUSE OF REPRESENTATIVES

MS. AL-JADDA: Thank you.

I want to thank you very much for having us here and on behalf of Mr. Kucinich I would like --

DR. SHAPIRO: You have to talk sort of closely into the microphone.

MS. AL-JADDA: I am sorry.

DR. SHAPIRO: You can turn the volume a bit if you want. There is a little knob there somewhere.

MS. AL-JADDA: Sure.

DR. SHAPIRO: Thank you. That is very helpful.

MS. AL-JADDA: Better.

DR. SHAPIRO: Yes, that is very helpful. Thank you.

MS. AL-JADDA: Great.

And I would like to thank you on behalf of Mr. Kucinich as well for these routine meetings and for having us here.

As Paul mentioned, there has been a flurry of activity on the Hill with regards to the oversight and the protection of human research subjects, which has in our view mainly focused on gene therapy and we have been researching this issue of oversight protection for the past year.

We have been looking at it from a more broader view with regards to all human research and that is the standpoint that -- where our bill comes from.

Two important things that H.R. 3569, Mr. Kucinich's bill, addresses is the current federal regulations or the Common Rule and the oversight mechanisms that are in place within the Federal Government.

We looked at OPRR as the main model for

oversight and we found that while the mechanism in place was appropriate, that there were many weaknesses in terms of support, financial support, and limited staff support as well, and so Mr. Kucinich wanted to bring that out and allow adequate resources for OPRR by making it an independent agency, and bringing it out of the NIH and separating it from the Department of Health and Human Services.

OPRR, we felt, still today, I understand they are to move OPRR out into the Office of the Secretary, we feel is still not an independent agency which, back then, and we still do now, feel that it is a conflict of mission. With it being in the NIH, OPRR is in -- is a regulator of human research and NIH is a funder of human research, and we felt that that -- there was a clash, perceived or real, there is a definite clash there.

However, we are encouraged by the Department of Health and Human Services to move it out of NIH and we definitely support that move as a move in the right direction.

Secondly, we wanted to address the issue of oversight in other departments and other federal agencies. We felt that there was inadequate oversight in the 16 other departments that do human research and there was a need to provide that oversight. That is excluding the FDA. Of course, the FDA has its own oversight mechanism which is very much in line with OPRR's, but different nonetheless.

So those were the two main goals of our bill and those were the two weaknesses that the bill addresses.

H.R. 3569 brings accountability for protecting human research by basically streamlining the oversight mechanism into a structured manner and it takes the authority from OPRR and brings it out into an independent agency which we would rename the Office for the Protection of Human Research Subjects.

We feel that this is something that is very needed and something that has the support of many in the bioethics community.

This umbrella agency would make accountable all other federal agencies that do not have oversight and that do have oversight, thus eliminating the perceived or real conflict of mission.

We also believe that OPRR, as its function within the Department of Health and Human Services, should not be eliminated and that this bill would not necessarily do that. It would not eliminate its functionary role as a disseminator of information.

The Interagency Coordinating Commitee created by our bill is -- would be made up of the heads of all the federal agencies that currently comply with the Common Rule. It would allow the heads to make recommendations on the Common Rule and have this office report back to Congress on how the Common Rule could be changed.

It would also give the authority to the Director of this office to change the Common Rule and make recommendations with respect to the exemptions of the Common Rule.

Lastly it would -- it does not talk -- it does not address IRBs or the make up of IRBs, which we did not want to address in our bill. We were aware of Mr. Waxman's legislation and we have been talking a lot about that and felt that his legislation and that of Representative DeGette's legislation were very -- was well addressed, the issue of IRBs, and so we specifically did not want to talk or address the issue of IRBs.

Our main goal here is to make a single agency, an independent credible agency with enough resources and accountability to protect human research subjects, and we believe that this need has been widely recognized.

And we look forward to the recommendations that NBAC makes in the future and hope to work with you in any way we can on the legislative proposals that we have.

Thank you.

DR. SHAPIRO: Thank you. And thank you very much. Let me thank both of you again for both your presentations and for the effort in coming here.

Let me turn now to see if there are questions from members of the Commission.

Yes, Alta?

DISCUSSION WITH COMMISSIONERS

PROF. CHARO: Thanks very much for coming.

Since Mr. Waxman is a cosponsor I guess I will direct my questions both you, Ms. Al-Jadda and Mr. Kim.

I wonder if you can clarify just a couple of points in the bill as I was reading through it where I was not sure I understood the intent behind the language.

First, with regard to the range of human beings who would be protected, the bill begins under 2801(b)(1) by saying that "The Director of this new office will establish criteria to protect human subjects..." and then it goes on to say "...in research conducted, supported or otherwise subject to regulation by the Federal Government."

I was not sure if you were intending through this to simply mimic the current scope of mandatory coverage of the regulations or if this was, in fact, a suggestion that any area that was eligible for regulation, for example, all human subjects research via the commerce clause would be covered by virtue of this bill so I was not sure if you were using this bill to extend human subjects protection as far as our resolution had suggested back in May of 1997 or not.

MS. AL-JADDA: Our intent was to extend its coverage to all federally funded research in all departments that comply with the Common Rule. So private research would be excluded from this bill.

PROF. CHARO: Okay.

The second is, if I may and then I will stop and yield the floor, Ms. Al-Jadda, you had suggested, I think I heard, something about the enforcement powers of this office but I am looking and I am not seeing the section in which the enforcement powers are spelled out exactly, and I just wondered if you could help direct me because I am seeing a great deal in the bill that is reminiscent of the way OPRR currently operates.

It is very collaborative, through an interagency coordinating committee, takes agreement among the heads of various agencies, and what I was not clear about was specifically the ability of this office to determine regardless of the attitudes expressed by people in other agencies to make certain changes in the basic regulations and, second, to enforce those changes as against other agencies or even against individual IRBs.

I just was hoping you would clarify whether it is here in the bill or if it is implicit in some portion of the bill.

MS. Al-JADDA: Right. We have given authority to the director to change -- to change the Common Rule, the federal regulations. We did not spell out how that would happen. It was something that we have left out in terms of the procedures of how it would be changed in terms of, you know, putting it into the Federal Register or receiving comments on it.

PROF. CHARO: If I can clarify. I would presume that the Administrative Procedure Act would be the basic --

MS. AL-JADDA: Right.

PROF. CHARO: -- governing statute with regard to how you actually change the regulation. It was not clear to me whether or not one would need the active support of all or a majority of the members of the Interagency Coordinating Committee or if this is something that could be done unilaterally by the director of the office --

MS. AL-JADDA: Right.

PROF. CHARO: -- where the coordinating committee is simply -- it is politicked to get their approval but it is not necessary.

MS. AL-JADDA: Right. That is correct. It is not necessary to get their approval but they would be giving recommendations to that.

PROF. CHARO: And in terms of enforcing against other agencies, it would have that authority.

MS. AL-JADDA: Yes.

DR. SHAPIRO: Thank you.

Tom?

Excuse me. Diane, you were first. I apologize.

Tom, you will have to wait a second.

Diane?

DR. SCOTT-JONES: Thank you both for coming.

I have a question for Mr. Kim. You mentioned in your presentation to us that you are especially interested in the special protections related to children, and I was wondering if you could say a little bit more about that and, in particular, of the current Common Rule, the special subpart on children has not been adopted by all the agencies that support or conduct research with children. So could you say more about your thinking about special protections needed for children?

MR. KIM: You have put your finger exactly on the -- one of the two sources of concern that we had regarding the subpart that even under federal funding was not a universal -- a question of universal application -- and obviously that is something we would like to see, but also to revisit them and to hope that if there have been changes in clinical practices or changes in standards that they might be reflected in revisions to the subpart as appropriate. And, hopefully, that will be a subject that the Commission could work its way towards addressing in this report.

But the second source of our concern was that we were -- the premise for our adoption in the FDA Reform Act of '97 of the pediatric drug provision, which encourages this research and encourages sponsors to conduct it, and then in exchange they get exclusivity, was that there be more research involving children.

And if we were putting a spur in place to this field of research, our hope was that the protections were in place and were at least adequate and reflected current practices.

Not having that assurance and not being aware of whether or not there is an activity within the Federal Government or outside in terms of specialty societies, the American Academy or others, we felt that this would be an appropriate venue or an appropriate way to address it in the whole context of human subject protections writ large and that some action would be taken in a timely manner.

We do not have a sense as yet as to precisely how much research is being conducted by the companies. We are just hearing back from the FDA as to the number of submissions they are receiving from companies to, you know, get the six months exclusivity in exchange for the additional approved indication for children, but our sense is that there is a great deal of activity and our hope is that we could work with bodies on the outside as well as the Commission in developing and understanding what needs to be done.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I would like, also, to ask you what your thinking is on research with adolescents as distinct from children who are younger than the teenage years. Right now the regulations on children apply to any person who is a minor and there has been quite a lot of discussion over the last few years about whether adolescents should be treated differently from children and yet differently from adults as well.

So have you given any thought to that?

MR. KIM: We have not but we are hoping other folks are. In fact, that is precisely the kind of change in practice and change in current thinking that we hope would be reflected in any changes to the subpart. We would not have any basis and expertise or experience to be able to make any recommendations, but hope that this will flow upwards and we will be able to take advantage of your work on that area.

I am not aware of any consensus as far as the fields or the specialties are with respect to the status of adolescence but, hopefully, that is something you can do for us.

DR. SHAPIRO: I think this point Mr. Kim was just making, namely we create a spur out there to include more children in medical experiments, is quite real. I do not know what the numbers are either but many researchers are talking to me about how they have to put together their panels in different ways and so on. So I think this is really a very important point for us to come back to at some point.

But, Tom, you had a question?

DR. MURRAY: Thank you, Harold.

I want to thank Ms. Al-Jadda for coming. It is great to see that Representative Kucinich of Cleveland is weighing in on this. I have been away for about a year now but still regard it as a very important place for us.

I am going to direct my question primarily to Mr. Kim.

I thought you gave an exceptionally incisive account of the key issues. I think I certainly have come to feel that human subjects research is under renewed challenge, the ethics of human subjects research. IRBs are overwhelmed and underfunded and undervalued within institutions.

Complex financing, private financing arrangements are becoming more the rule than the exception with all sorts of potential, both individual and institutional possible conflicts of interest.

Something must be done to ensure the safety and protection of human subjects and to ensure public confidence in the research enterprise.

Would you be open to more -- to call them radical is to maybe over emphasize it, but to sort of broader reconceptualizations of how to enhance the protections for human subjects such as, for example, as some other nations have done. Ensure that the committees that review research are more independent of the institutions under which the research takes place and increasing the number of lay people, of average citizens, looking over the research subjects.

Do you think there would be an openness to that sort of consideration should NBAC recommend it?

MR. KIM: Those are precisely the questions that we have in mind when we think about not only IRB workload and administration, but also composition and membership. Those are very important questions in our minds and we recognize that the academic research community will argue back, and appropriately so, that this is an additional responsibility taken on voluntarily by participants, that it is difficult to incentivize participation, and the workload itself is so extreme that it can take away from other essential responsibilities.

But at the same time I do not think there is any aversion to some open thinking about this topic precisely because opening up of participation on IRBs to the lay public -- maybe by changing the specifications in the Common Rule, or requiring different standards -- that would be responsive to different forms of research we are also very open to. And recognizing that there is a diversity of research involved and recognizing there is a diversity of research settings.

And on the final point you mentioned the complexed financing. I just wanted to add that the for-profit IRBs was a subject addressed by the GAO. I think it is not very clear to us precisely how that is influencing, if at all, the conduct of review by IRBs, what sort of participation, what sort of uptake in terms of research being evaluated by these kinds of IRBs is taking place depending on source of funding.

We are very interested in getting to those questions and there is a great deal of fact finding that has yet to be done and we will have to perhaps seek that from either the administrative agencies or from the investigative bodies like GAO.

DR. MURRAY: Thank you.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Thank you to both of you.

This is directed to Mr. Kim.

With respect to the applicable -- broadening the applicability and scope of the Common Rule, as the previous speakers indicated, there is really two ways one thinks about broadening the scope.

The first is to extend it to research which is not currently covered because of the funding source or -- not just that but because most of the private research, if it goes through the FDA, is covered that way regardless of the funding source, but rather because broadening the scope of what is considered human subjects research.

You did not have that in your list. I wondered if it was something that was also on your list.

And then the second question, and it ties to what we were just talking about, is we imagine -- so to speak, what are the sources of harm that are arising? They can arise from activities which are, in fact, currently covered by the scope but it is not being appropriately done.

Second would be, it should be covered because -- and it is, in fact, not being covered because of the funding source.

And the third is because it is not being considered human subjects research.

Do you have a sense right now of where in those three is the major problem or is it a matter of still not having the facts?

MR. KIM: I do not mean to abdicate responsibility by saying we just do not have the facts, but the appeal of the simple is to cut the pie along the lines of funding source and saying, well, this research simply falls out because it is not federally funded or it is not at federally funded institutions. For us, the appeal of extending the rule -- the Common Rule and the protections in that manner was almost intuitive at this point, and that is the appeal there.

The types of research which are not covered or which are not protected is also a question of great interest to us, and we do not have the facts but it is in a way a function of this -- the other way that you cut scope and who is -- who does not apply.

We have heard the arguments that there are significant burdens attendant to trying to expand the scope of protections to privately funded research, and part of that debate has already taken place in the

context of privacy.

What we are very interested in trying to obtain and trying to ascertain are precisely what kinds of research currently are not protected and currently fall outside of the Common Rule because of its private funding. If it is going to the FDA under an IND then clearly it is captured. If it is conducted at a federally funded academic medical -- it is covered.

What we do not understand and the extent of our knowledge really reaches only to things like *in vitro* fertilization, perhaps. What other research is being conducted that does not fall under the protections? We do not have a good sense of that. It may be that it falls below the threshold of minimal risk and, therefore, you know, would be exempted. But we are very interested in trying to get that information and we are not certain how the best way to go about that is.

We anticipate that there will be claims that confidentiality or trade secrecy might attend to disclosing that kind of information, but I think in the interest of moving this debate forward there has to be a full disclosure by research funders, whether they be private or public, as to what they are doing.

We do not have an answer to that and I think that is why we have not discussed raising or broadening the protections in that manner.

DR. SHAPIRO: Okay. I will take the last question from Larry.

DR. MIIKE: Am I correct in assuming that the focus of the concerns in the Congress are primarily in the clinical care and physical harm area and not so much in health services research, public health research and survey research?

MR. KIM: I think that is a fair statement if only because it is what we are familiar with and have a body of experience to work from.

More often than not an anecdote can have a very powerful effect on our thinking, and many of the anecdotes in many of the unfortunate incidents in human subjects research are those which involve clinical research and so that is I think the main spring for our concerns.

But part of the process of education on the Hill will certainly be information that you can share with us and findings that you will have regarding other fields of research and where there might be potential abuses and the need for protections. Things that we probably have not even gone into as far as thinking is concerned.

DR. SHAPIRO: Thank you very much.

Well, first of all, I really hope that you will convey to Congressman Waxman and Kucinich our appreciation for the fact that both of you are here. More importantly, for their interest in this area, which is of great interest to us.

We began this project in the overview of human subjects protection formally about a year ago and, as you know and as you indicated, in our reports we have taken on certain aspects of this now. We are now in the midst of our comprehensive report.

We would hope you will tell both Congressman Waxman and Kucinich that we would be delighted to be helpful in any way as we go ahead. We would certainly like to participate in hearings if and when those -- it is decided that those are appropriate and help out really in any way that we can to move us to perhaps a better spot than we are right now.

So, once again, thank you both very much for coming. I am aware it is a little outside of where you normally are sitting. It is a little bit of a ride up from D.C. here and we appreciate your efforts in coming.

Members of the Commission, unless there is any other business we will adjourn.

Thank you. We are adjourned.

(Whereupon, the proceedings were adjourned at 2:43 p.m.)

* * * * *