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38th MEETING
NATIONAL BIOETHICS ADVISORY COMMISSION

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1 P R O C E E D I N G S

2 OPENING REMARKS3 HAROLD T. SHAPIRO, Ph.D.

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

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

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

19 The human gene therapy research is simply the
20 first panel.

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

24 Alternative federal regulatory systems will
25 be the third panel.

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

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

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

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

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

22 Marjorie?

23 ETHICAL AND POLICY ISSUES IN THE OVERSIGHT
24 OF HUMAN SUBJECTS RESEARCH
25 OVERVIEW OF WORK TO DATE

1 MARJORIE A. SPEERS, Ph.D.

2 DR. SPEERS: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

24 The fourth panel addresses issues related to
25 the definition of research. Today specifically in the

1 area of health services. At the January meeting you
2 heard about problems of applying the definition of
3 research to public health and today you will hear
4 about the gray areas in the definition related to
5 health services research.

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

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

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

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

25 I want to really do just two things to

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

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

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

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

25 So that will be our focus as we go through

1 not only this panel but other panels that deal with
2 human subjects protection in particular areas.

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

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

11 Thank you very much for being here today.

12 PANEL I: OVERSIGHT OF

13 HUMAN GENE THERAPY RESEARCH

14 CLAUDIA MICKELSON, Ph.D., CHAIR,

15 RECOMBINATION DNA ADVISORY COMMITTEE

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

18 DR. SHAPIRO: Certainly.

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

21 DR. SHAPIRO: Okay.

22 DR. MICKELSON: And I will stay to time.

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

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

1 here.

2 (Slide.)

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

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

16 (Slide.)

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

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

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

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

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

13 (Slide.)

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

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

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

1 research.

2 At the local institutional level all of the
3 responsibilities of institutions for protection of
4 human subjects in human gene therapy is also outlined.

5 OPRR looks at the structure of the Institutional
6 Review Boards. The NIH Guidelines look at the
7 structure and responsibilities of Institutional
8 Biosafety Committees. And the investigators fall --
9 and have responsibilities for all three groups.

10 (Slide.)

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

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

22 And the Institutional Biosafety Committee has
23 responsibility for all of the intermediate steps
24 leading up to the human gene transfer, the development
25 of a human gene transfer clinical trial because that

1 role is outlined in the NIH Guidelines.

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

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

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

19 (Slide.)

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

24 (Slide.)

25 The NIH Guidelines -- I am going to go

1 through each three of those very quickly.

2 The NIH Guidelines apply to all projects,
3 whether they are funded by NIH or not, that involve
4 recombinant DNA technology and is conducted at or
5 sponsored by institutions that receive NIH support for
6 any projects involving such techniques.

7 Institutions and investigators, therefore,
8 that receive NIH monies must comply with the NIH
9 Guidelines. That is stated directly within the NIH
10 Guidelines. And that impinges on then privately
11 funded research or industry sponsored research that
12 has been conducted at an NIH institution.

13 The institution then has an obligation to
14 ensure compliance with the NIH Guidelines and that
15 means all submitting and reporting responsibilities
16 that are outlined in the guidelines. It then becomes
17 the institution's responsibility to ensure that the
18 trial is conducted in accordance with the NIH
19 Guidelines.

20 (Slide.)

21 The role of the NIH Recombinant DNA Advisory
22 Committee is the protection of patients, the public,
23 the community and the environment. That is throughout
24 all of the responsibilities of the Institutional
25 Biosafety Committee. The committee is also involved

1 in policy development which is then expressed in
2 changes to the Recombinant DNA guidelines.

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

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

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

21 (Slide.)

22 The Office of Biotechnology Activity
23 coordinates the activities of the committee,
24 coordinates our oversight activities and policy
25 development. They also are responsible for protocol

1 management, development and maintenance of a database,
2 as well as establishing and running and organizing for
3 the committee Gene Therapy Policy Conferences, as well
4 as they are the actual execution arm for our education
5 and public and industry interface.

6 (Slide.)

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

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

10 (Slide.)

11 I am speaking a little quickly to stay within
12 15 minutes or so. I apologize.

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

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

1 (Slide.)

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

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

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

15 (Slide.)

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

19 Delivery -- the largest -- most of the
20 research involves use of some type of defective virus
21 to deliver genes to the humans, whether it is injected
22 directly into the patient or whether cells are removed
23 from the patient and then the cells are infected and
24 then reintroduced into the patient. That is the ex
25 vivo treatment where cells are removed and then

1 transduced with a viral vector. It is the route of
2 administration for most of the trials that use
3 retrovirus.

4 Adenovirus, which is one-quarter of the
5 clinical trials use adenovirus as its delivery system.

6 Adenovirus tends to be used more *in vivo*. It is
7 given directly to the patient usually by direct
8 injection into tumor.

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

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

21 Again we would expect to see some of the
22 newer -- you can tell from the literature which
23 vectors are in the pipeline and will be coming forward
24 to clinical trials and those -- once safety issues are
25 resolved -- would probably -- we would probably see

1 things like lentiviral vectors and/or attempts to
2 correct defects *in situ* with repair.

3 (Slide.)

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

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

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

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

25 (Slide.)

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

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

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

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

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

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

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

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

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

22 The other issues are -- these are fairly
23 standard and we see them repeatedly but issues of
24 persistent and regulated transgene expression and then
25 the potential -- we look at secondary effects of

1 insertion of any DNA into the genome can have effects
2 on neighboring genes.

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

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

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

9 (Slide.)

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

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

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

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

24 And the issue of *in utero* gene transfer, the
25 RAC policy is that any attempt to do *in utero* gene

1 transfer at the moment is premature. We do not know -
2 - there is not enough basic science known about
3 development in embryos nor is there enough control
4 within the vectors but that it was not a ban. The
5 words were used that it was "premature."

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

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

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

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

25 The way I approach it is that there -- we can

1 reach agreement on what types of therapies and uses
2 are not enhancement which could be the least upper
3 bound of the problem. There are areas that we could
4 agree upon that are -- would be enhancement and that
5 could be the greatest upper bound.

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

11 If we could go on then to skip the next one
12 and on to the NIH oversight of gene transfer research.

13 I will rush through the origin and evolution.

14 DR. SHAPIRO: May I interrupt?

15 DR. MICKELSON: Yes.

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

18 DR. MICKELSON: That is all right.

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

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

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

25 DR. MICKELSON: Surely.

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

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

7 The current protocol review process, which is
8 probably --

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

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

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

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

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

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

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

13 (Slide.)

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

21 (Slide.)

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

24 Each investigator receives a letter that
25 gives the outline of the RAC review and the public

1 discussion and reiterates the necessity to comply with
2 the guidelines and the reporting of adverse events.

3 (Slide.)

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

11 (Slide.)

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

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

1 (Slide.)

2 In order to try to address this issue of lack
3 of approval and to enhance the NIH/RAC review process,
4 the NIH committee proposed a change to the NIH
5 Guidelines that had to deal with the timing of
6 submissions so that the NIH committee could review
7 protocols before the local committees had completed
8 their review process so that the NIH committee would
9 review protocols that had at the same time that they
10 were being submitted and reviewed by the local
11 institutions. This would be before the FDA process of
12 review or initiation -- the IND could go forward
13 because institutional review board approval would not
14 have occurred so that the RAC review would occur
15 before patients could be enrolled and the trial
16 started.

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

22 (Slide.)

23 It would avoid multiple layers of a
24 synchronous review and it would ensure that patients
25 that were not consented -- that patients could not be

1 consented and enrolled in a novel research protocol
2 prior to the public discussion and the RAC review.

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

7 (Slide.)

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

11 (Slide.)

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

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

20 (Slide.)

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

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

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

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

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

18 (Slide.)

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

23 Also, we will attempt to enhance and further
24 use web accessible submissions and a web -- and create
25 the web accessible database so that not just the

1 public is aware of what is the status of current
2 trials but that patients can also access information
3 on the status of trials.

4 (Slide.)

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

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

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

15 DR. MICKELSON: Any questions?

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

19 DR. MICKELSON: Sure.

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

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

25 Thank you very much for coming.

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

3 LANA SKIRBOLL, Ph.D., DIRECTOR

4 OFFICE OF SCIENCE POLICY,

5 NATIONAL INSTITUTES OF HEALTH

6 DR. SKIRBOLL: Is it on?

7 DR. SHAPIRO: It is on.

8 DR. SKIRBOLL: I think it is on.

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

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

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

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

25 There are many things that NIH has been doing

1 well in this arena. I know recent news reports have
2 suggested that this -- there is considerable problem
3 with this oversight but let me just recall briefly to
4 you that our mandate is public discussion.

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

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

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

22 And we, most importantly, held a public
23 meeting. One that I think you all read about in one
24 form or another in which scientists, the public and
25 the press could all come together, hear about this

1 research, hear what the facts were with regard -- both
2 with regard to the death of Jesse and in particular
3 the safety of adenoviral vectors. Again an important
4 service, I think, to both the research community and
5 the public.

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

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

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

24 We need to make sure that when patients are
25 in research, of course, that we minimize risk to those

1 subjects and we do that through a variety of ways,
2 both the system and most importantly through what we
3 are calling informed consent.

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

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

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

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

24 It can be related to the treatment but it can
25 also be due to underlying disease. And, as you know,

1 and I hope we have made it clear that with regard to
2 adverse events in gene therapy many of the patients
3 here are quite sick. They are at endstage disease.

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

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

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

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

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

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

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

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

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

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

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

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

22 I hope I was short enough and not too fast.

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

1 Let me now turn to Dr. Zoon.

2 Dr. Zoon?

3 KATHRYN C. ZOON, Ph.D.

4 DIRECTOR, CENTER FOR BIOLOGICS EVALUATION

5 AND RESEARCH, FOOD AND DRUG ADMINISTRATION

6 DR. ZOON: Thank you.

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

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

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

24 While we will spend today discussing gene
25 therapy, really many of the issues that the agency

1 deals with, with gene therapy, are very similar to all
2 the other biological products that the agency
3 regulates. Probably the major difference that I would
4 say is our dual role with the NIH and the RAC in the
5 oversight of gene therapy products.

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

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

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

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

1 of the exponential growth in this area.

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

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

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

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

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

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

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

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

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

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

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

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

25 We look at the animal studies. What are the

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

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

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

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

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

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

5 If, in fact, when the agency is reviewing an
6 IND they have any concerns, major concerns on the
7 safety of a trial, the trial will go on clinical hold.

8 And this go on -- a clinical hold can take place if
9 the initial study protocol -- we believe there are
10 safety risks to the patients or after the trial is
11 ongoing and certain adverse events take place.

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

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

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

25 Any findings that we see in animal laboratory

1 testing that may have a significant risk for humans
2 must be reported to the FDA within 15 days.

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

6 The agency may decide to change the
7 eligibility criteria to exclude patients at high risk.

8 They may change the dose route of administration and
9 the schedule of administration. They may change the
10 informed consent to add -- to disclose the new
11 toxicities. They may ask for additional consent from
12 study participants to reflect the new information.

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

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

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

1 particular circumstances.

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

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

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

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

23 A number of documents have been developed on
24 quality, safety and efficacy as a result of this
25 process but of particular importance and relevance to

1 this case is a good guidance document which is dealing
2 with good clinical practices, which it talks about
3 clinical monitoring, informed consent, et cetera.

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

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

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

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

23 In addition, the FDA has a bioresearch
24 monitoring program. The agency is going to be
25 enhancing as resources permit our looks at clinical

1 investigations underway, particularly in the gene
2 therapy area.

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

8 Why are we doing that?

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

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

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

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

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

8 Thank you.

9 DISCUSSION WITH COMMISSIONERS

10 DR. SHAPIRO: Thank you very much.

11 Let me thank all members of the panel.

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

19 Alta, and then Larry.

20 PROF. CHARO: Thanks very much.

21 NBAC has over the years written reports that
22 have recommended the creation of a national body to
23 exercise review over special areas that pose special
24 concerns. We have done this in the report on people
25 with impaired capacity to make decisions. We have

1 done it with regard to the report on embryo research
2 and stem cell research.

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

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

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

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

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

3 DR. SHAPIRO: Lana?

4 DR. SKIRBOLL: A good question.

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

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

23 From that perspective it is important.

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

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

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

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

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

21 Is the system perfect? No, it is not perfect
22 and I am not sure -- it is only because the system is
23 not perfect or the public perception is not perfect.
24 The goals and the mandated missions of the NIH and FDA
25 in this oversight, I think, are correct. I would not

1 change the goal. I would not change the regulatory
2 authority of FDA over this area. They do a great job
3 and they do it thoroughly. NIH should not be held
4 responsible for regulatory authority over this arena.

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

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

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

21 DR. SHAPIRO: Thank you.

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

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

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

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

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

19 DR. SHAPIRO: Thank you.

20 Larry?

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

24 (Laughter.)

25 DR. SHAPIRO: I am always ready for last

1 year's vacation, too.

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

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

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

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

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

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

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

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

16 Many of the protocols that we see because of
17 the length of time it takes during development -- we
18 see many protocols that, in fact, use almost
19 essentially the same vector but in slightly different
20 patient populations and given the history that most of
21 the protocols are still in Phase I there are many
22 important biological issues that are not being
23 addressed and we would like to encourage greater
24 scientific quality and use of the clinical trials so
25 that the data -- and to -- for -- to urge the

1 investigators to obtain more information from these
2 trials and then use those back into basic science
3 studies so that the next round of clinical trials that
4 we see are better.

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

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

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

22 But it was basically to stop the committee
23 from reviewing protocols that had already started and
24 enrolled and treated patients so that the public
25 concerns and scientific and ethical issues could be

1 gotten in at an earlier phase.

2 DR. SHAPIRO: Thank you.

3 Rhetaugh?

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

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

11 DR. SKIRBOLL: Well, I think --

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

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

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

23 Some of the issues that I described to you --
24 when we get a serious adverse event, all those things
25 that we do and look at as a result of a serious

1 adverse event that is unexpected and associated with
2 the product will be dealt with.

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

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

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

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

1 it is a very dynamic interactive process.

2 Lana, did you --

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

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

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

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

25 DR. SHAPIRO: Rhetaugh, is this very short?

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

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

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

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

21 DR. SHAPIRO: Thank you.

22 Tom?

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

25 I suspect most of us would agree certainly on

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

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

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

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

25 And, thirdly, that -- and most importantly

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

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

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

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

23 DR. ZOON: Could I comment?

24 DR. SHAPIRO: Yes.

25 DR. MICKELSON: I just wanted to comment I do

1 agree with Dr. Murray. I think it is absolutely
2 essential that adverse event data be in the public
3 realm, that it be put in its proper context but having
4 adverse event data and clinical results or results
5 from the clinical trials in the public realm I think
6 is absolutely fundamental to the future of the field.

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

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

21 However, scientific information and the
22 results of trials when put into an arena that patients
23 and other scientists can access, that has been long
24 recognized as -- it is equivalent to a scientific
25 publication. There should be no reason to hold this

1 information as confidential. It has been marked
2 confidential when submitted to the RAC and we have
3 fought through the Office of General Counsel to remove
4 that label so that it can be accessed.

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

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

17 DR. SHAPIRO: Thank you.

18 Dr. Zoon, very short.

19 DR. ZOON: Yes.

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

22 DR. ZOON: Very short. One point of
23 clarification when FDA has a problem with gene therapy
24 or any other therapy that it believes it transcends a
25 given protocol, the FDA has the ability to identify

1 other protocols as well as contact those and put those
2 other trials on clinical hold, and that has to be done
3 in real time to protect the patients.

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

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

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

13 DR. MICKELSON: Yes.

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

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

19 Bernie?

20 DR. LO: Thanks. I want to shift the focus
21 of attention for a minute. You have been talking
22 about sort of what is novel about gene therapy and NIH
23 has talked about how the RAC looks at things like *in*
24 *utero* therapy and germ line therapy. FDA is talking
25 about novel sort of vectors and viruses. But it

1 seems to me that a lot of the problems that may be
2 going on are not cutting edge. They are sort of old-
3 fashioned.

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

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

21 There is a whole mind set and a whole
22 interaction process that really sets up the
23 misconception and confusion and it seems to me all
24 these sort of complex systems you have worked out or
25 working out do not really get to that problem, which

1 at least in the public discussion of this event adds
2 confusion, and it seems to me again it is both on the
3 part of the investigators and the potential
4 participants.

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

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

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

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

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

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

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

23 DR. SHAPIRO: Thank you.

24 Alex?

25 PROF. CAPRON: The question that I want to

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

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

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

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

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

1 report.

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

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

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

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

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

17 The noncompliance with reporting was to the
18 NIH Guidelines, not to the FDA regulatory
19 requirements. So with regard to real time analysis of
20 those adverse events and patient protections that data
21 had been reported to the regulatory agency.

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

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

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

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

9 MR. HOLTZMAN: May I --

10 DR. SHAPIRO: Steve, just a second. Steve,
11 if this is really just information here, okay, because
12 --

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

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

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

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

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

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

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

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

1 DR. PATTERSON: Sure.

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

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

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

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

23 Now we hear that there are severe problems in
24 the RAC not hearing from the FDA about these hundreds
25 of adverse events over seven years that were

1 apparently new to you, the way that they have been
2 reported here, and that is only for adenoviruses, and
3 I gather we have not had an equal beating of the
4 bushes as to any of the other recombinant DNA
5 experiments.

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

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

23 Has this given you any thoughts about what
24 needs to be done vis-a-vis the IRB system, which is
25 the more basic form of protection of subjects if for

1 all we know, as far as I know, it was not -- are you
2 finding that the IRBs at these institutions where
3 these 652 unreported events occurred knew about them
4 and had not told you about them or were they equally
5 in the dark?

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

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

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

21 PROF. CAPRON: Let me --

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

25 PROF. CAPRON: Yes.

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

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

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

20 PROF. CAPRON: And will your inquiries that
21 are going on now tell you the answer to that question?

22 That is did the local data and safety monitoring
23 board, institutional biosafety committee and IRBs in
24 the institutions which reported to you these 652
25 adverse events have knowledge of those events and had

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

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

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

18 DR. SKIRBOLL: We are conducting not for
19 cause site visits different than the FDA. We are
20 going out to institutions to make sure that
21 institutions know of the existence of the NIH
22 Guidelines, are following the guidelines, know what
23 their roles and responsibilities are with regard to
24 reporting to the NIH. We are not, the NIH is not,
25 investigating IRB oversight.

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

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

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

24 DR. SKIRBOLL: That is a question perhaps you
25 should address to OPRR. The NIH does not -- the RAC

1 does not go out -- we have -- the investigators are
2 responsible to report to us. We are going out and
3 making sure they have processes in place but we are
4 not investigating whether those adverse events went
5 appropriately to the IRB. We do know they went
6 appropriately to the FDA and that, where appropriate,
7 FDA made changes.

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

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

14 DR. SHAPIRO: Okay.

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

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

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

21 Steve, you can use any part of two minutes.

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

24 Steve, you have two minutes.

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

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

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

15 Okay.

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

22 DR. SKIRBOLL: Can I just make one statement?

23 I think blink and it is going to change because there
24 is a RAC working group looking at adverse event
25 reporting with the goal of harmonizing what is

1 required by the RAC and the Food and Drug
2 Administration so that we will not have the kind of
3 confusion that you are describing.

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

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

12 DR. MICKELSON: Okay.

13 MR. HOLTZMAN: All right.

14 DR. MICKELSON: All right.

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

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

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

23 (Laughter.)

24 DR. SHAPIRO: Thank you very much.

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

1 I really want to thank the panel very much.

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

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

7 Thank you all very much.

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

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

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

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

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

22 MS. RUSSELL-EINHORN: Is this on?

23 DR. SHAPIRO: That is on and what we are
24 dealing here with is the case of revising of the
25 expedited review categories in the case of classified

1 research, which is -- that is right. It is under tab
2 3E, as you can see, in your agenda.

3 MS. RUSSELL-EINHORN: Okay.

4 DR. SHAPIRO: I apologize for keeping you
5 waiting.

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

8 Thanks for the opportunity --

9 DR. SHAPIRO: That would be great.

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

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

24 DR. SHAPIRO: Yes.

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

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

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

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

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

23 The two examples -- actions that I have been
24 asked to discuss: One is called the "interim final
25 rule pertaining to additional protections for human

1 subjects in classified research," and that is what I
2 am going to begin with.

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

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

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

22 We started off by drafting this as something
23 called the "Notice of Proposed Rulemaking." That
24 means that we would take a proposed rule, put it in
25 the Federal Register, probably ask for comments during

1 a period of 90 days, get those comments, review them,
2 integrate them and then publish a final rule.

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

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

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

1 not have an interest in signing?

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

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

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

21 And so we took back the NPRM from the
22 agencies. We reformatted it as an interim final rule
23 and an interim final rule means that it would get
24 published in the Federal Register. It would be
25 effective immediately but we would still take comments

1 on it so the public would have an opportunity for
2 input and at a later date we would integrate and
3 change the interim final rule if necessary.

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

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

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

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

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

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

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

24 So who can change the expedited review list?
25 This is a very different process than trying to have

1 an interim final rule on classified research taking
2 the form of an amendment to the Common Rule.

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

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

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

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

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

6 We thought this would be a worthy addition to
7 the process so we did so anyway and in November of
8 1997 only nine months after we began the revision
9 process we published a proposed list for public
10 comment in the Federal Register.

11 We had a 120 day comment period. We received
12 108 comments, which is quite different from the 22,000
13 comments, which I understand the Stem Cell Council has
14 received. So the 108 were actually very easy to deal
15 with. We revised them.

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

22 To summarize, there have been these two
23 actions recently. These are the only actions
24 involving -- regulatory actions involving the Common
25 Rule. One is an attempt to amend the Common Rule. We

1 require -- we have to get the signatures of 15
2 agencies.

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

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

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

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

21 Let me now turn to the Commissioners for
22 questions.

23 Any questions about this?

24 Larry?

25 DISCUSSION WITH COMMISSIONERS

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

4 (Laughter.)

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

8 DR. SHAPIRO: Rhetaugh?

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

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

16 DR. DUMAS: Okay.

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

19 DR. SHAPIRO: Not at all.

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

24 DR. DUMAS: Okay. Thank you.

25 DR. SHAPIRO: Thank you.

1 Any other questions from Commissioners on
2 this issue?

3 Yes, Alex?

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

7 (Laughter.)

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

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

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

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

1 University of Pennsylvania.

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

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

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

24 What I am concerned about as I hear this is
25 we have already learned that despite the expectation,

1 which I think is implicit in the NIH Guidelines for
2 Recombinant DNA that there will be communication
3 between FDA and NIH, and despite this fact that the
4 FDA and NIH have now said that from now on they will
5 make sure that communication does, indeed, exist, it
6 did not exist and NIH was learning -- FDA was learning
7 stuff that NIH should have known and did not know.

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

23 DR. PUGLISI: That is --

24 PROF. CAPRON: Nevertheless, I gather they
25 are supposed to be part of the annual reporting

1 process. Even ones that are not unanticipated should
2 be part of the annual reports that IRBs review.

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

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

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

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

23 Secondly, I can give you some anecdotal
24 information. I have conducted or have been involved
25 with probably 40 site visits to institutions where we

1 had identified problems over the last ten years.

2 I can tell you in every one of those site
3 visits we felt that investigators were not reporting
4 unanticipated problems to the IRB in a timely fashion.

5 It is a problem everywhere as far as I can tell from
6 the anecdotal experience that I have.

7 DR. SHAPIRO: Well, it seems --

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

10 DR. PUGLISI: We have done that, yes.

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

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

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

21 I mean, it is just completely obvious in that
22 we ought to -- we do not have all the numbers but --
23 and that would be helpful if we knew more but whether
24 we have those numbers or not it is quite clear at
25 least on the basis of what people have appeared before

1 us that this is really a serious problem.

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

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

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

16 The second dimension was unanticipated. Alex
17 has mentioned that.

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

25 Number three, the third level is associated

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

24 DR. ELLIS: One brief response. A direct
25 response to Larry's specific question. In 1996, I

1 personally begged the White House Domestic Policy
2 Council to make the classified research change by
3 presidential order and the White House legal counsel
4 said they did not believe they had the authority to do
5 that and that is why they went this route.

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

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

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

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

24 (Laughter.)

25 DR. ELLIS: I asked.

1 (Laughter.)

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

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

7 Eric?

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

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

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

19 (Whereupon, a break was taken.)

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

25 Let me turn to Marjorie to introduce this

1 panel.

2 Marjorie?

3 DR. SPEERS: Thank you.

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

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

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

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

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

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

20 Ms. Flack?

21 PANEL III: ALTERNATIVE FEDERAL

22 REGULATORY SYSTEMS

23 DIANE FLACK, M.S.

24 SENIOR HEALTH PHYSICIST, RULEMAKING AND

25 GUIDANCE BRANCH OFFICE OF NUCLEAR MATERIAL

1 SAFETY AND SAFEGUARDS,

2 NUCLEAR REGULATORY COMMISSION

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

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

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

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

16 (Slide.)

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

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

1 (Slide.)

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

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

11 (Slide.)

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

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

23 The question arose of whether they should
24 create separate agencies to promote and to regulate
25 civilian uses of nuclear energy and this concept

1 gained particular support during the era of oil
2 embargo and energy crisis of 1973-74.

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

7 (Slide.)

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

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

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

24 (Slide.)

25 How do we accomplish this mission? We have

1 several different components.

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

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

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

10 (Slide.)

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

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

19 (Slide.)

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

25 With the Part 35 example that we are

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

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

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

19 (Slide.)

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

1 executive branch.

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

4 (Slide.)

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

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

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

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

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

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

10 (Slide.)

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

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

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

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

1 facilities.

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

7 (Slide.)

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

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

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

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

25 What did it do? It coordinated radiation

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

7 (Slide.)

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

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

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

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

25 So those -- I think that is a good way for

1 different agencies to work together.

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

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

14 There is a history of regulation, "The first
15 25 years of NRC." There are two documents on the two
16 different interagency committees and one which --
17 unfortunately it is my only copy right now but I would
18 be glad to have them xeroxed -- is a document that I
19 co-authored which are across the board radiation
20 protection standards and guides.

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

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

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

7 Ms. Ley?

8 That is it. You are on.

9 JANE LEY, J.D.

10 DEPUTY DIRECTOR FOR GOVERNMENT

11 RELATIONS AND SPECIAL PROJECTS

12 OFFICE OF GOVERNMENT ETHICS

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

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

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

1 basis.

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

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

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

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

23 So they were -- it covered a much broader
24 range of misconduct. Not something that you would get
25 thrown into jail for doing, but something they just

1 did not think at least executive branch employees
2 should engage in that kind of conduct.

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

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

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

22 Now, as you can imagine, there became --
23 there was wide disparities in the interpretation and
24 enforcement of the very same words, agency by agency.

25 I mean, in the area of gifts -- now over a few years

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

6 In 19 -- basically as a result of Watergate -
7 - I think we were created as a response to "you have
8 got to do something more than just prosecute people."
9

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

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

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

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

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

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

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

23 We provide it to the ethics officials and the
24 ethics community and we provide it to employees when
25 they find us. And the phone directory, they kept

1 losing us for years, nobody could, you know, publish -
2 - the Bell Telephone said we did not or whoever, the
3 phone company said we did not exist.

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

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

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

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

1 regulations they had in place.

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

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

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

21 We issued a proposed regulation -- well,
22 first of all, we started with a number of meetings
23 with all the ethics officials. We tried to get some
24 sense of where everybody was. We had a new executive
25 order. We finally issued a set of proposed

1 regulations and we got over 1,000 comments. Most of
2 which came from inside the government but some of them
3 did not.

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

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

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

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

1 head of an agency.

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

5 The same is true if an agency is not properly
6 -- is refusing to take action or cannot take action
7 for some reason with regard to an individual employee.

8 At that point we have to go to a public hearing and
9 we have to have a public hearing about the conduct of
10 the individual employee and we still simply make a
11 recommendation to the President.

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

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

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

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

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

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

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

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

23 I presume the President -- whether we were
24 created by statute or not, I assume the President
25 could have established us as a part of his -- some

1 group within the White House given his basic authority
2 to deal with the conduct of federal officials.

3 So those were the ways in which we got going.

4 DISCUSSION WITH COMMISSIONERS

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

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

10 Alta?

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

14 Ms. -- is it Ley?

15 MS. LEY: Yes.

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

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

23 Historically, what has been the experience
24 with OGE's success at having agency heads, in fact,
25 enforce as vigorously as OGE might like to see and

1 providing the resources OGE thinks are necessary since
2 OGE has no direct line authority over the agency heads
3 or the departmental secretaries?

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

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

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

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

25 We have not found -- we have found one agency

1 that tanked just because they took all the resources
2 away from the ethics program. The program tanked,
3 and that was the Department of Agriculture, and we
4 went in there and they have really beefed that back
5 up.

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

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

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

20 DR. SHAPIRO: Thank you.

21 Alex?

22 PROF. CAPRON: I have a question for each of
23 you. I think a common theme in the presentations has
24 been the ability to act that arises when you have
25 responsibilities and connections with departments but

1 you can act without waiting for them all to sign on.

2 You were probably here when we heard an earlier
3 presentation about the difficulty of getting the
4 Common Rule modified.

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

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

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

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

1 inspection, enforcement.

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

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

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

23 PROF. CAPRON: The question for Ms. Ley is
24 clearly you are in a position from what you have
25 described and I would take from the description in the

1 materials we got of the role of the committee that you
2 can even get more deeply, it says, in limited
3 circumstances investigate possible ethics violations
4 and order corrective action.

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

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

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

25 We were initially exposed early on to

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

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

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

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

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

1 send all those forms to?

2 MS. LEY: Yes.

3 (Laughter.)

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

6 DR. SHAPIRO: Larry?

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

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

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

20 What is the size of your budget?

21 MS. LEY: \$9.1 million.

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

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

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

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

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

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

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

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

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

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

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

4 DR. SHAPIRO: Thank you.

5 Ms. Flack?

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

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

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

25 DR. SHAPIRO: Thank you.

1 The last question, Alta.

2 PROF. CHARO: Thank you.

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

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

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

25 Having spent the last three years working

1 very closely with all the medical specialty boards and
2 trying to respond to their questions and making sure
3 that their input is in the new regulations, I think
4 there is quite a bit of openness right now.

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

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

20 So I think it works very, very well.

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

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

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

9 Thank you.

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

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

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

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

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

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

23 I do not want to repeat all that but we are
24 very fortunate this afternoon to have two people who
25 will speak to us really in the area of health services

1 research, that particular aspect of the issue.

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

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

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

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

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

17 PANEL IV: DEFINITION OF RESEARCH

18 ANDREW NELSON

19 EXECUTIVE DIRECTOR, HEALTH PARTNERS AND PRESIDENT

20 HMO RESEARCH NETWORK

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

25 DR. SHAPIRO: If I could say we think of

1 ourselves as rock stars here, which means we have to
2 talk close to the microphone. It works best.

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

5 (Laughter.)

6 DR. SHAPIRO: That is true.

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

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

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

20 Staffed with over 150 career researchers and
21 1,200 FTE's of research support staff, they conduct
22 public domain research that is really dominated by
23 health services research.

24 Federally funded projects represent more than
25 50 percent of the \$92 million that support their work.

1 DR. DURHAM: Thanks very much.

2 We consider this a great opportunity to talk
3 to this group about a type of research that may be
4 less commonly thought of than men in white coats, men
5 in lab coats. Sometimes we think of it as men in no
6 coats and ties. And that is a kind of research that
7 has been going on and developing for probably the last
8 25 to 30 years.

9 And really health services research, which we
10 would like to talk about today, had its beginning in
11 academic organizations under variously titled
12 departments like "medical care organization" or
13 "health systems" or various titles like "medical
14 care."

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

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

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

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

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

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

19 Let me give you an example. The Rand Health
20 Experiment -- Health Insurance Experiment -- in the
21 1980's looked at a variety of ways of financing health
22 care, but when it came time to look at the outcomes,
23 things like hospital care, the use of specialists and
24 so forth was the major purpose of that inquiry.

25 Now these are systematic research studies and

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

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

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

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

21 The health care systems that Andy was
22 describing in the HMO Research Network are primarily
23 integrated health care systems funded by capitated
24 financing, and under capitated financing arrangements,
25 providers or health care systems have no incentive to

1 provide treatments that are not effective or medically
2 necessary.

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

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

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

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

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

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

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

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

10 So health plans have got to find ways to
11 identify women who are at high risk for breast cancer.

12 They must help people try and stop smoking. And so
13 they -- and they also may be required by employers who
14 sponsor their employees to be our members to meet
15 quality standards set by the National Council on
16 Quality Assurance, so-called NCQA, or other purchasing
17 coalitions.

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

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

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

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

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

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

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

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

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

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

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

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

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

25 On the other hand, quality improvement is

1 proprietary. The QI activity will launch a program or
2 improve an existing system for the benefit of the
3 population it serves.

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

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

18 The second concept I would like for you to
19 consider is what I call "agent." Quality improvement
20 is done by someone within the organization and it is
21 usually initiated by someone on the quality
22 improvement team. Projects that are initiated by an
23 outside person, even if that outside person or entity
24 is a business partner, kind of like is defined by the
25 HIPAA regulations, that research -- that constitutes

1 research to me. And so the agent of the work is very
2 important.

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

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

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

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

1 with internal funding.

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

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

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

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

25 For example, if a scheduling clerk is trying

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

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

18 So I will turn it over to Andy.

19 MR. NELSON: Thank you.

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

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

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

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

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

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

23 The first is the increasing state and federal
24 regulations that we see coming at us. The second is
25 the adequacy of the Common Rule definition and the

1 application of regulations in reviewing health
2 services research.

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

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

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

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

1 are being asked.

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

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

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

23 And many of the investigators are also asked
24 to be on the IRB because they are the wellspring of
25 knowledge about that area and so it promotes knowledge

1 back into the research community at the same time.

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

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

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

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

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

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

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

25 If we had in addition to the common reviews

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

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

17 The types of studies that can cause extended
18 review by an IRB often are the registries, the
19 surveys, and the types of studies that are
20 noninterventional but involve vulnerable populations.

21 And our IRBs can spend extended times talking about
22 all of the different harms which come from disclosure
23 that are not necessarily physical harms.

24 Finally, I think that the definition of the -
25 - in the Common Rule is ambiguous and the regulations

1 between the agencies differ but IRBs understand this
2 intent from our experience and they are able to make
3 firm and informed judgments.

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

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

16 Thank you.

17 DR. SHAPIRO: Thank you.

18 Thank you both very much.

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

21 Alex?

22 DISCUSSION WITH COMMISSIONERS

23 PROF. CAPRON: Has the HMO Research Network
24 developed such guidance as to the definitions of
25 research because your article uses the word "research"

1 to -- as far as I can tell -- encompass some of the
2 things that Mary was describing as quality improvement
3 activities and in your closing remarks you just
4 described the need for a definition. I wonder if you
5 had in the private sector agreed among your HMO
6 colleagues in the Research Network on such a
7 definition.

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

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

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

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

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

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

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

25 Then once they are -- and that would trigger

1 the IRB for us. We would always do that.

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

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

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

25 DR. DURHAM: Well, those three things that I

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

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

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

17 DR. DURHAM: Yes.

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

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

25 DR. SHAPIRO: I would like to pursue this

1 point just a little bit to help my own understanding.

2

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

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

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

25 But do you think that perhaps looking at it

1 not by, as Alex and you were just talking about,
2 intent, agent, funding source,
3 systematic/nonsystematic, those are all useful and I
4 think maybe they are the correct ones, but what about
5 just focusing attention on where conflicts exist where
6 you have something other than the immediate health
7 needs of the patient in mind or potential conflicts?
8 That is right. Conflicts or potential conflicts. Is
9 that useful or is that not useful?

10 DR. DURHAM: Well, I think -- it is hard to -
11 - I do not know exactly where you are going with that.

12 I think that the thing that I fall back to in that
13 distinction -- we are always trying -- every -- all of
14 the research would also fall -- I think what I am
15 hearing you say is all of the research that we do
16 would certainly fall under the improvement of care.

17 DR. SHAPIRO: Right.

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

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

24 DR. SHAPIRO: Right.

25 DR. DURHAM: -- therefore, if such a thing

1 happened it would require for us to ask people if that
2 was okay and get their consent in order to be involved
3 in it. If it is for the direct benefit that is where
4 the conflict comes in because it becomes harder to
5 distinguish between what is -- what we ought to be
6 doing anyway.

7 The thing that presents wonderful conflicts
8 for us is the fact that external funding agencies,
9 people outside of our organizations, know that we can
10 generate new knowledge within it and so, therefore --
11 and very appropriately -- federal regulations that
12 have to do with research come our way.

13 If we lived in a world where there was not an
14 external funding source, I feel like we would need to
15 do this work anyway, and, in fact, there has not been
16 a lot of funding for health services research until
17 recent years.

18 My research organization is 37 years old and
19 so we were patching it together over all those years,
20 often with external funding. But even if we did not
21 have internal funding the conflict comes from the fact
22 that we need to do it some way some how.

23 DR. SHAPIRO: Thank you.

24 Bernie?

25 DR. LO: I want to thank both of you for a

1 very clear and well organized presentation. It
2 strikes me as I listen to you that your organizations
3 in your network have real commitment to making sure
4 that projects that might pose ethical concerns or
5 risks for patients are reviewed by someone other than
6 the researcher, usually an IRB-type mechanism.

7 I have two questions to follow-up on that.

8 One, as I look at the list of people that
9 responded to your survey, they are pretty much the
10 established HMOs. Many are nonprofit. Many are staff
11 model.

12 What do we know about the -- the first
13 question is -- what do we know about the willingness
14 of the aggressive for profit organizations that do
15 many of the same types of work, that may involve less
16 than usual care and the other criteria that Dr. Durham
17 mentioned? What do we know about the scrutiny that
18 they put those projects under?

19 Is it similar to what your organizations do?

20 And secondly is the resource question. And
21 both of you very rightly pointed out the economics of
22 health care and the era where costs seem to be rising
23 again and employers do not want to raise premiums too
24 much, what sort of institutional support do you give
25 to your IRB that does so much work?

1 You spoke, for instance, of volunteers. Are
2 clinicians who are on your committee given time off or
3 do they do it after hours? What kind of staffing?
4 What kind of budget do you allocate?

5 MR. NELSON: I will take the first question.

6

7 On the survey when we went out -- and this
8 was not a thorough survey of every managed care
9 organization in the country -- rather it was a search
10 of the literature.

11 It was a knowledge base of people who had
12 engaged in research and the people that they knew
13 engaged in research. We found 50 organizations that
14 claimed to be doing research.

15 DR. LO: I may not have made my question
16 clear.

17 MR. NELSON: Okay.

18 DR. LO: It was not the research, but it was
19 the things that use health service research techniques
20 for quality improvement areas, but which do it in ways
21 that both you and Dr. Durham suggested ought to
22 undergo the same kind of scrutiny and, in fact, do
23 within your organizations.

24 Is similar scrutiny put in place in other
25 people that do not publish the research and,

1 therefore, were not included in the surveys you did?

2 MR. NELSON: There may be single
3 investigators out there in those organizations. From
4 my knowledge and our background in this work, we are
5 not familiar with any organization out there beyond
6 this group of 20 that actually claimed to be doing
7 public health research.

8 DR. LO: All right. It is not that they are
9 doing research. They are doing QI that meets your
10 other --

11 MR. NELSON: QI, yes.

12 DR. LO: -- criteria.

13 MR. NELSON: I understand.

14 DR. LO: Your organizational --

15 MR. NELSON: Yes. And the oversight of that
16 -- there is an absence of knowledge. I do not know of
17 -- no. Do you know?

18 DR. DURHAM: No, I do not know.

19 The second part about the IRB support, I can
20 address that. It is all over the board in terms of
21 how organizations like our's -- once again, I do not
22 know about organizations unlike our's. But our's are
23 supported by the research enterprise -- by the
24 organization, the parent, the host organization.

25 And, also, because IRB is an essential

1 function of doing research when dollars come in for
2 research projects, indirect dollars are generated
3 which are then used to support the IRB but the models
4 themselves vary.

5 For example, IRB -- the Common Rule is very
6 clear about who -- that people need to sit on -- the
7 physicians, people with knowledge about research and
8 so forth, most of it -- I will make a bold statement
9 here that most of it is really volunteer work.

10 Sometimes honoraria are given to people but
11 it -- given the number of hours they work in a single
12 year on this it is a very small matter.

13 Physicians are very often given release time
14 to participate on IRBs. We use retired physicians --
15 and this is probably a good comment.

16 Many of our retired physicians love to come
17 and sit on our IRB because they have time to devote to
18 this activity whereas people who are practicing have
19 far greater difficulty getting time away from their
20 clinical schedules to participate. So we have had
21 wonderful experiences with recently retired physicians
22 who give a huge number of hours.

23 MR. NELSON: Our experiences that we have had
24 long-term members both from the physician staff and
25 from the community, but we need to pay our chair and

1 vice chair because they really have to spend a good
2 chunk of time reviewing all studies.

3 DR. SHAPIRO: Thank you. We have three
4 people. I will ask again given the time to keep
5 questions and responses as brief as possible.

6 Tom, and then Jim, and then Larry.

7 DR. MURRAY: Hi. What you did today was both
8 encouraging and somewhat discouraging.

9 The encouraging part was it is good to know
10 that there are leaders of the field such as yourselves
11 who are so thoughtful about this and I think trying to
12 do the right thing.

13 It is discouraging for those of us who are
14 trying to figure out how to operationalize a
15 definition of research that would be applicable,
16 readily understandable, and most importantly capture
17 what is morally significant to the public about what
18 is special about research and the protections that we
19 should accord subjects.

20 Mary, you gave us three. Funding source,
21 agent and intent. I am going backwards because intent
22 is the most promising but I think even that in some
23 sense fails.

24 Funding source could come internally or
25 externally or out of your own pocket, but it could

1 still count as research. That is true in university
2 settings. It is true in HMOs.

3 Agent: You could hire an outside Beltway
4 bandit or consulting firm to come in and do a QI study
5 that was not at all generalizable. I mean, I am not
6 sure that the agent is going to work.

7 Intent is the one that is hopeful, but even
8 that is a problem because -- I think, Mary, you told
9 us that sometimes you do a QI study really intending
10 it to be a QI study but it is really interesting and
11 you want to publish it. Was it research? Not in the
12 initial intent but in its -- ending up being used as
13 generalizable knowledge, yes.

14 One little wrinkle might be what if all
15 journal editors -- what if all journals and editors
16 agreed that they would not publish any study using
17 human beings, whatever its announced initial intent
18 was, if it did not go through appropriate IRB review
19 even if it would -- and whatever. I do not know if I
20 am being very clear here.

21 In other words, if I did a QI study and it
22 did not go through the IRB, loved my results, wanted
23 to publish them but I could not get them published, it
24 would no longer -- it would not be generalizable
25 knowledge. I mean, that is just a little possible

1 wrinkle.

2 DR. DURHAM: One of the problems with that --
3 I mean, it is good to be -- we want to be able to
4 transport knowledge from one place to another. We
5 want to be able to do quality improvement.

6 One of the -- a couple of things that
7 concern, I think, most of us who have been talking
8 about this within organizations is that we do not want
9 people to be so daunted by the review process that
10 they will stop doing the work and this could very well
11 happen. They could say it is not worth the IRB-style
12 review.

13 And that is why at least within my
14 organization, the HIPAA rules that were just published
15 by the Secretary in calling for a privacy officer,
16 that we do not object to something of that sort if we
17 can use the judgment of that kind of person or a
18 quality council or some other entity.

19 The second point I want to make here is that
20 there is grave concern on the part of IRBs that it is
21 going to be even more confusing to pile quality
22 improvement projects that are meant for the -- you
23 know, for the use of the organization into the review
24 list, not only due to volume -- and I agree it could
25 cripple the IRBs ability to do its work but also --

1 and also drive off the people who have very kindly
2 volunteered for this work but now the work would be
3 threefold and fivefold beyond what it is currently
4 doing.

5 So I am quite serious. People love to do
6 work that is quality improvement, in organizations I
7 have found, but there is just so much that they will
8 do to -- you know, do paperwork and get reviews done
9 that they might not choose to do and so there is a
10 balancing act here.

11 DR. SHAPIRO: Thank you.

12 Jim?

13 DR. CHILDRESS: Thank you. Your
14 presentation and the discussion that has followed have
15 been very helpful, I think, in showing us some of the
16 dangers and pitfalls that we face in trying to sort
17 out this whole area.

18 Two quick questions. One is in the health
19 plans that you are familiar with, is there any kind of
20 disclosure up front about quality improvement
21 activities whether they are called research or not?

22 That is the first question, and even though
23 such a general consent might not be adequate from say
24 an ethical standpoint, still it would be useful to
25 know if that is present in the health plans.

1 And then second in the discussion of privacy
2 and confidentiality that was fairly brief in your
3 comments and focused mainly, Mr. Nelson, more on the
4 problems of the state laws that might impose a lot of
5 restrictions in this area, but what kinds of concerns
6 have been expressed within both quality improvement
7 work and research that goes on about privacy and
8 confidentiality within the organization?

9 So two parts of the question.

10 DR. DURHAM: Do you want to take the first
11 one and I will take the second one? The notice part.

12
13 MR. NELSON: Yes. There is a common notice
14 that is in a health plan contract with a member that I
15 am aware of, at least in our two organizations, that
16 when a member joins they are notified that we do
17 conduct research and that we do use records.

18 We will ask them if they are involved in any
19 study at all individually that we will ask them about
20 that study through a consenting process. So we do
21 have those disclosures and there are notices up front
22 but it is not adequate in terms of individual study
23 involvement.

24 DR. DURHAM: And other organizations that I
25 have been associated with have had "Patient Bill of

1 Rights" kinds of things for consumers, and in it one
2 of the points will be that we do research, but it is
3 not something that is on -- posted on every medical
4 office wall, although we are usually recruiting for
5 studies and there is some kind of notice on virtually
6 every clinic's board about that.

7 The second question about confidentiality --

8 DR. SHAPIRO: Go ahead. Do you want to press
9 your button, Jim?

10 DR. CHILDRESS: Sorry. Thank you.

11 Okay. The notice up front about research.
12 So the question is when you are talking about IRB
13 review, are you also assuming then that you will want
14 consent on the part of people who are participating in
15 it, because your movement to the IRB is again not
16 constrained by the requirements of the Common Rule, as
17 you were talking about, but your felt need to get some
18 additional input into the evaluation of the protocol?

19 So I guess I am not quite clear. This
20 consent up front to research would be different from
21 consent up front, and I am using the term "consent"
22 loosely here knowing all sorts of constraints for the
23 people to really have a choice and so forth.

24 Is that -- are you -- when you were talking
25 about this notice and you used the term "research,"

1 both of you used it, were you including under that
2 quality improvement? I mean, was that at this point a
3 very broad category, not a specific category?

4 MR. NELSON: If it meets the definition.

5 DR. DURHAM: Well, the information would be
6 conveyed both that we do quality improvement and
7 research and then when it is research or some of that
8 quality improvement the IRB, of course, requires that
9 we get informed consent and we do so. So it is a
10 multilayered process.

11 DR. SHAPIRO: Thank you.

12 Larry?

13 Jim, I am sorry.

14 DR. CHILDRESS: If they could deal with the
15 privacy and confidentiality question.

16 DR. SHAPIRO: I am sorry. I apologize.

17 DR. DURHAM: We are very concerned about
18 making sure that quality -- that confidentiality and
19 privacy are very strongly inculcated into our world.
20 I will tell you why. This sounds like apple pie and
21 motherhood, but it is really true.

22 Unlike a university, where you might put out
23 a newspaper ad to recruit subjects for research,
24 people are members and so we are very careful not to
25 approach them and ask would they like to be

1 participants in studies so frequently that it is
2 burdensome or that we -- and that we maintain this
3 research relationship with them.

4 And so we want to make sure that we have
5 standards for research that go beyond what the federal
6 requirements require because of that relationship with
7 them.

8 And so I think that we have taken steps far
9 in advance of other researchers because we have to
10 nurture that continuing relationship with people so we
11 are very concerned and we want to be there and beyond
12 in each of these instances.

13 MR. NELSON: Two examples of that. One is
14 that not just for federally funded research but we
15 review all research with the same standard.

16 Second that most -- in Mary's case all of the
17 health services research studies which would be
18 required to go through only an expedited process are
19 going through a full review process.

20 DR. SHAPIRO: All right, Jim?

21 DR. CHILDRESS: Yes.

22 DR. SHAPIRO: Larry?

23 DR. MIIKE: It seems that what you are trying
24 to do is responding to the universe that IRBs look at,
25 which is research activities.

1 But if you forget for a minute that boundary
2 of research and trying to be flexible around how you
3 compare quality assurance studies versus research, it
4 seems to me that the major concerns that would be
5 raised would be conflict, consent, safety, privacy and
6 confidentiality.

7 So that if we could redesign a system that
8 focuses more on the risks inherent in any system
9 rather than on the definition of research and if you
10 could balance it off so that you do not end up with an
11 IRB that has gotten more things added on to it, would
12 it make sense to have a review regardless of whether -
13 - especially in the kind of organizations you have,
14 which is not concerned so much about whether it is a
15 research project or quality assurance, but whether
16 looking at these issues of -- and in your case most of
17 your studies do not really deal with safety in
18 classical physical safety issues -- so you are
19 basically dealing with conflict, consent, privacy and
20 confidentiality.

21 Would that simplify your system for you?

22 DR. DURHAM: I am presuming that -- I am
23 trying to imagine what it would look like. It would
24 be minimum risk or minimum necessary -- minimum. Just
25 thinking of minimum risk as the concept and then all

1 comers would be reviewed if it was more than minimal
2 risk. Could I make that assumption?

3 DR. MIIKE: Except that I am not sure if
4 privacy and confidentiality would be considered
5 minimal risk.

6 DR. DURHAM: Right.

7 DR. MIIKE: Am I right?

8 DR. DURHAM: It might. It would certainly be
9 a useful tool for us. Right now we are kind of
10 overlaying that and, in fact, that whole concept of
11 minimal -- I am using the term "minimal risk" as
12 really the reason that we bring more into the IRB than
13 we are required to because we are saying we want to
14 take a very narrow view or very broad view really of
15 what might conceivably constitute risk.

16 I do not think I have answered your question.

17 MR. NELSON: For a research organization to
18 monitor a whole health care organization and the
19 quality improvements and the medical staff and all the
20 clinics would be impossible and so we really have to
21 look to the greater organization to have this privacy
22 officer function, a compliance officer and the
23 regulatory compliance process.

24 So there really needs to be a much greater
25 responsibility there than just a research

1 organization.

2 DR. MIIKE: But it seems to me that if you
3 have one body that focuses on the issues I mentioned,
4 conflict, consent, privacy and confidentiality
5 basically in your organization, you soon develop an
6 institutional memory within a given body rather than
7 having --

8 MR. NELSON: This is true.

9 DR. MIIKE: -- I mean, you heard -- if you
10 were here earlier you heard what is happening in all
11 these different areas where you have privacy laws, you
12 have the IRB system.

13 MR. NELSON: Yes.

14 DR. MIIKE: You know, all of those kinds of
15 things and it is so scattered that no one really has a
16 grasp on it and it seems that -- I am just asking
17 whether that might not seem a reasonable alternative
18 if we can get around the issue about what is a
19 research project.

20 DR. DURHAM: I think so. I mean, it would be
21 a more -- it would be a way to pull it all together
22 and it would have to recraft to the IRB system because
23 it is too big and it is too much for the people who
24 currently -- and it might also be a different set of
25 rules that are applied once you got -- once you have

1 gathered those projects together.

2 You might need to look at research which is
3 not going to contribute to the care of that individual
4 right now, which we are calling research, and the
5 Common Rule calls research, versus something that is
6 quite different.

7 It takes a different level of skill perhaps
8 to scrutinize those two different things even if you
9 pulled them together in one place.

10 DR. SHAPIRO: Thank you.

11 The last question will be from Rhetaugh.

12 Rhetaugh?

13 DR. DUMAS: I just wanted to make an
14 observation because I had some real question about
15 where to draw the line between what you are calling
16 research and what you are calling everything else. I
17 think that is where the critical issue is.

18 There are issues of safety and risks involved
19 in the enterprise's business to people and that there
20 is a temptation to ask what you are doing about that
21 but that is not our primary concern.

22 We are concerned with research risks and so
23 the definition of research for me becomes a very
24 critical issue and I have a hard time distinguishing
25 between -- even with your criteria -- between what you

1 are calling research and what you are calling quality
2 improvement.

3 I gather that that is something that you
4 probably continue to struggle with.

5 DR. DURHAM: Right.

6 If we -- if we cannot -- if the people
7 responsible for research like Andy, and I cannot
8 decide and if we are face to face with a quality
9 improvement person in our organization, and I think it
10 is research and that person thinks it is quality
11 improvement, it has to be adjudicated by, let's say
12 the medical director, and he or she has to make a call
13 based some organizational memory and some decision
14 rules that we have developed.

15 So I know that all the organizations in the
16 HMO Research Network have been hammering away to help
17 that medical director, who is going to adjudicate
18 this, how to make that call, but it comes to -- a lot
19 -- most -- many of them fall easily into one camp or
20 another but there is a number in the gray zone and
21 those decisions are made on a case by case basis.

22 I am saying I simply do not know how to do it
23 other than looking at those case by case distinctions.

24 DR. DUMAS: Right. One more comment, though.

25

1 I have a great deal of difficulty with the
2 criteria of intent because a person may not intend
3 that they are doing research and yet all of the other
4 mechanisms in the process would fit the criteria for
5 research in my definition.

6 DR. SHAPIRO: Well, thank you.

7 First of all, I have -- well, thank you.

8 And I was going to make a gratuitous comment
9 at the end.

10 I want to thank you first because that is the
11 more important part. You really have brought out for
12 us some of the really key issues that we are
13 interested in and I very much appreciate your efforts
14 and your willingness to come down here and speak to
15 us.

16 I have admired over time a great deal of the
17 research that has come out of organizations such as
18 your's, and have read it and am grateful to you and
19 your colleagues for having produced it.

20 Now comes the gratuitous comment as an
21 economist. That is why this sort of does not count.
22 You can consider this meeting almost adjourned.

23 If it were true, as I said before, the
24 overuse, underuse, and misuse were the driving
25 incentives for these organizations, no expense would

1 be spared for IRBs if you needed it. It is just not a
2 -- we hear this all the time from everybody who does
3 research and it just seems to me that is a disconnect.

4

5 That is a gratuitous comment and it does not
6 need any response but it is something you might think
7 about as you think about it.

8 Well, let's be -- I understand that our next
9 panelists are not yet here. Is that still correct?

10 In that case let's take a 10 minute break and
11 try to reassemble at five after.

12 (Whereupon, at 1:53 p.m. a break was taken.)

13 DR. SHAPIRO: I would like to get our meeting
14 underway again.

15 Our next and final panel today is an attempt
16 to bring Commissioners up-to-date on some important
17 initiatives in Congress and very fortunately we have
18 two important staff people out here spending some time
19 with us today.

20 It is Paul Kim and Souheila Al-Jadda.

21 One is -- of course, Paul, as you know, is
22 with Congressman Waxman's office.

23 And Souheila is with Congressman Kucinich, as
24 you all know, from the House of Representatives.

25 Paul, I think you are going first.

1 Welcome.

2 Thank you very much for taking time to be
3 with us today.

4 PANEL V: UPDATE ON CONGRESSIONAL INITIATIVES

5 PAUL T. KIM, J.D., M.P.P., COUNSEL

6 CONGRESSMAN HENRY A. WAXMAN,

7 UNITED STATES HOUSE OF REPRESENTATIVES

8 MR. KIM: Thank you very much, Dr. Shapiro.

9 Can everybody hear me?

10 DR. SHAPIRO: It actually works a little
11 better if you use the one on your right and just pull
12 it towards you a little bit and push the button. It
13 will turn -- a red light will go on.

14 MR. KIM: Great. Is that better?

15 DR. SHAPIRO: That is better. Thank you.

16 MR. KIM: Great.

17 DR. SHAPIRO: We think, as I said before, we
18 think of ourselves as rock stars. You have to stay
19 close to the microphone.

20 (Laughter.)

21 MR. KIM: Thank you very much for the
22 invitation to appear on behalf of my employer,
23 Congressman Henry Waxman.

24 We are delighted that the Commission is
25 meeting on a regular basis and is conducting its

1 evaluation of human subject protections in the United
2 States.

3 As a matter of historical interest, Mr.
4 Waxman has always been a very strong supporter of the
5 previous work of previous national presidential
6 Commissions, and our hope is that in the near future
7 we might actually encourage congressional interest in
8 authorizing on a permanent basis a Commission of this
9 kind to avoid the kind of pendulum of interest that
10 has swung back and forth as different Commissions have
11 been authorized and then fallen out of activity only
12 to find a period of inactivity at a period of
13 importance where bioethical issues are not being
14 scrutinized on a national level.

15 So this is a -- just to begin, that is an
16 issue of great interest to our office and we believe
17 to other offices as well on the Hill.

18 One of the reasons we are very, very
19 encouraged by the Commission's activities in human
20 subjects protections broadly is I think congressional
21 interest is at a high at the moment -- certainly in
22 the past few years. And it is in no small part
23 because of the previous work products that the
24 Commission has generated, the reports on stem cells
25 and on cloning, for example.

1 The enforcement actions by OPRR recently have
2 also been a trigger for congressional interest. The
3 disclosures in the media about clinical research
4 practices, including patient recruitment.

5 Those have also been a spur to congressional
6 scrutiny but to date it has not manifested in formal
7 hearings or compulsory hearings, but our hope is that
8 with the completion of the Commission's report on
9 human subject protections that might well be the basis
10 for formal congressional action on this topic.

11 One of the issues that our office has taken a
12 great interest in of late has been in the field of
13 gene therapy research. It is a subject that I know
14 you discussed extensively in this morning's session,
15 and I will not repeat or go over territory you have
16 already gone over but we find it notable that on the
17 25th anniversary of Asilomar we find ourselves
18 addressing very much the same questions that were
19 tackled then, by many of the same participants in the
20 debate, which is also of note to us.

21 But we think that some of the failures in
22 oversight, institutional oversight and in regulatory
23 oversight in gene therapy research are notable because
24 they have great relevance to human subject protections
25 elsewhere in other fields of research.

1 From what we understand from data given to us
2 by the NIH and FDA and from the media accounts of some
3 of the problems with gene therapy research there have
4 been clear failings on the part of principal
5 investigators and on the part of IRBs and different
6 institutions in adhering not only to the NIH
7 Guidelines but also to 45CFR46.

8 We have noted with great interest that the
9 private sponsors of much of this research have to date
10 taken a very legalistic approach to their obligations
11 under current regulations, insofar as they have
12 claimed that responsibilities for adhering to the NIH
13 Guidelines, at least, stop at the institutional door
14 and that the private sponsors, in having a legal
15 obligation to comply with the guidelines, had no
16 responsibility as far as due diligence was concerned
17 to ensure that the investigators that were sponsoring
18 were also complying. We see that as -- if not a
19 loophole, then certainly a future topic for scrutiny
20 and oversight.

21 Finally, there have been well-documented
22 problems in regulatory oversight by the FDA and NIH.
23 You have probably seen all the materials that have
24 gone back and forth between Congress and the agencies.

25

1 You have undoubtedly seen or reviewed the
2 transcript for the subcommittee hearing on the Senate
3 side, but we think most notable as far as FDA's
4 actions were concerned was their failure to
5 communicate in a timely manner with the RAC and with
6 the NIH regarding compliance with the NIH Guidelines
7 when they had such a substantial body of information
8 and when they were serving as *ex officio* members.

9 That kind of failure, I think, is extremely
10 disturbing to us. We can only hope that it is truly
11 unique and does not reflect upon the FDA's oversight
12 of clinical research through the IND process.

13 And as far as the NIH is concerned, we do
14 understand that you have heard about the prospective
15 changes that the Administration will take on in the
16 next few weeks to, hopefully, remedy these problems,
17 but it was the truly unprecedented failure in adverse
18 event reporting, the scope and the variety of
19 noncompliance, which we have documented, which was
20 truly surprising to us and we hope will be remedied
21 very, very shortly.

22 But that kind of failure again we felt went
23 to at least, in part, a change or a perception of
24 conflict of culture in the NIH between its funding
25 mandate and its responsibilities to oversee this

1 research.

2 That was made clear to us directly by the
3 agency in their communications and so it is not as if
4 it is a question in doubt. It is something that they
5 recognize as being something that needs to be worked
6 on.

7 As far as the public attention that has been
8 paid to gene therapy, there has only been one
9 documented death attributable to an experimental
10 therapy and we are very well aware of the potential to
11 over react, to overstep as far as Congressional action
12 is concerned, but we would hope that we could take
13 this opportunity and that the Commission will use this
14 as an opportunity to hammer on the fundamental
15 importance of compliance with human subject
16 protections, that the NIH Guidelines are only one
17 manifestation of those kinds of protections, and that
18 we should use this as a good opportunity as a stepping
19 stone to reforms and to enacting meaningful changes
20 that will assure that there is a zero tolerance
21 culturally, as well as in practice in the field, and
22 that the agencies do take their oversight
23 responsibilities as seriously as possible.

24 I want to make a quick comment about what our
25 office is working on currently. Although there have

1 been no hearings in this past session of Congress on
2 human subject protections, we are working on
3 legislation.

4 And the reason we are is not because we
5 intend to overstep or anticipate what the Commission
6 is doing or what Congress might do by ways of
7 oversight hearings, but because we believe that many
8 of the problems with human subject protections are
9 well documented.

10 There are the GAO reports, the Inspector
11 General's report, and of course the Advisory
12 Commission on Human Radiation Experiments. We noted
13 their findings with great interest as well several
14 years ago.

15 If it is at all helpful to you I could walk
16 very quickly through some of the problems we perceive
17 and need to be addressed and welcome the opportunity
18 to hear from you through your questions, as well as
19 areas where you think our attention should be
20 directed.

21 But, in brief, the first and foremost problem
22 obviously is the application and scope of the Common
23 Rule protections and of the additional subparts under
24 45CFR46, the vulnerable population protections.

25 We cannot see any argument in equity or

1 principle why there are some subjects of human
2 research who are not protected by these standards and
3 there are others who are. And that that disjunction
4 is simply a function of funding source that to us does
5 not make any sense, and we would welcome any
6 argument from any parties on -- in the field or from
7 other stakeholders, as to why that is an appropriate
8 distinction but we believe that is one that should not
9 stand and should be remedied quickly.

10 We have in our discussions with stakeholders
11 heard about the potential burdens of extending the
12 Common Rule and the vulnerable population protections,
13 but we have not seen any reasonable calculation of
14 what that burden would be or what the additional
15 resource constraints would be on institutions and
16 whether that would be overly burdensome.

17 Again, taking -- bearing in mind that there
18 is a powerful argument in equity for extending the
19 protections, and we believe that any additional costs
20 would be justified by those arguments.

21 We are concerned about and took note of the
22 report, the Commission's report on individuals with --
23 and I hope this is the appropriate term -- impaired
24 decisionmaking capacity.

25 We noted that there are -- there is a need to

1 revisit the additional protections under the -- not
2 the Common Rule, but the other subparts, and we are
3 looking particularly at the protections as they apply
4 to children, given the implementation by the FDA of
5 incentives for additional pediatric research and their
6 own regulation in that regard. We think that is an
7 area that should be examined in great detail.

8 We are very concerned about the deficit of
9 information regarding informed -- regarding IRBs and
10 the extent to which the institutions are complying
11 with the NIH Guidelines and with the Common Rule. We
12 do not know how many IRBs there are, what standards
13 they adhere to in terms of education or the adequacy
14 of training for their members.

15 We are certainly concerned in trying to
16 obtain some sense of the number of subjects who are
17 involved in the research and what categories of
18 research they are involved with.

19 We are very cognizant of the work loads that
20 the IRBs have currently and the need perhaps for
21 additional resources, whether they be institutional or
22 federal resources, to insure that they are doing their
23 job appropriately.

24 We have seen the literature on informed
25 consent and took note of the NCI's recent actions to

1 streamline or make their informed consent forms more
2 understandable.

3 The whole notion that the informed consent
4 process should be truly informed. We are willing to
5 be educated about some of the deficits in that process
6 and hope that the Commission's report can contribute
7 to our better understanding of what needs to be done
8 to make informed consent work more appropriately.

9 We are interested in the questions of
10 disclosures to patients, not only the conventional
11 categories of information that are disclosed to them
12 through informed consent, but what are things such as
13 financial conflicts of interest. Investigator
14 conflicts are appropriate categories of research -- of
15 information to be shared with the patients, in what
16 contexts and what kind of information would be truly
17 useful to them in making informed decisions.

18 And finally we have applauded the movement of
19 OPRR to the Office of the Secretary. We believe that
20 will help them carry out their job in a more effective
21 and efficient manner but we are very interested in
22 seeing whether the resources available to OPRR are
23 adequate, whether there are other forms of sanctions
24 that might be appropriate short of the withdrawal of a
25 multiple project assurance for institution.

1 We have heard criticism of OPRR on that
2 score, but to be frank, we are not sure what one can
3 do as a federal regulator when there is widespread
4 noncompliance at an institution. We would welcome
5 your scrutiny of that question and see if there are
6 any contributions or suggestions you might have as to
7 what might be other sanctions that could be used in
8 this area.

9 The legislation we are working on currently
10 is with Congresswoman Diana DeGette, and our hope is
11 that there will be bipartisan and bicameral interest
12 in sponsoring it. We have already seen -- had
13 expressions of interest from the Senate as well as the
14 House and from both parties. Obviously this is not a
15 partisan issue and it is our hope that that will be
16 true when we introduce the legislation.

17 And finally let me just emphasize again that
18 we are looking for with great, great interest the
19 findings and the recommendations that the Commission
20 will have. It is something that we intend to carry
21 forward with and, if at all possible, we might hold
22 the introduction of the legislation in abeyance until
23 we have had an opportunity to review and incorporate
24 your suggestions into any legislation.

25 Thank you.

1 DR. SHAPIRO: Well, thank you very much. I
2 appreciate it.

3 We will hold questions for the moment.

4 I just want to make a few comments in
5 response to some of the things that you have said.

6 We certainly would like to participate in any
7 way that is helpful with initiatives on the Hill that
8 we can contribute to and we are very anxious to
9 contribute to something that will deal with problems,
10 which I think we know are out there that need to be
11 dealt with.

12 We are very grateful, of course, for not only
13 Congressman Waxman, but a bipartisan group of people
14 have been very supportive of initiatives in this area
15 over time, of which Congressman Waxman is certainly
16 one.

17 I do want to say just for point of
18 information, is regarding the scope of the Common
19 Rule, that NBAC has been on record for the last three
20 years since 1997 saying that we believe that is a
21 problem and so we certainly share your view of that
22 and I think we increasingly share your view regarding
23 the deficit information regarding whether IRBs,
24 institutions, investigators and so on are meeting
25 their responsibilities under current rules and

1 regulations, let alone those that might come up.

2 And we are certainly focusing on that as well
3 as on the last item you mentioned, that is OPRR, which
4 has gone through one transformation now, and the
5 question is whether that is the right one and so on.

6 Those are all issues which we share and I was
7 really very interested to hear your own perspectives
8 on that and very grateful for that.

9 If you do not mind, we will just go on and
10 hear from your colleague and then we will see what
11 other questions there are.

12 Ms. Souheila?

13 SOUHEILA AL-JADDA

14 LEGISLATIVE AIDE

15 CONGRESSMAN DENNIS J. KUCINICH

16 UNITED STATES HOUSE OF REPRESENTATIVES

17 MS. AL-JADDA: Thank you.

18 I want to thank you very much for having us
19 here and on behalf of Mr. Kucinich I would like --

20 DR. SHAPIRO: You have to talk sort of
21 closely into the microphone.

22 MS. AL-JADDA: I am sorry.

23 DR. SHAPIRO: You can turn the volume a bit
24 if you want. There is a little knob there somewhere.

25 MS. AL-JADDA: Sure.

1 DR. SHAPIRO: Thank you. That is very
2 helpful.

3 MS. AL-JADDA: Better.

4 DR. SHAPIRO: Yes, that is very helpful.
5 Thank you.

6 MS. AL-JADDA: Great.

7 And I would like to thank you on behalf of
8 Mr. Kucinich as well for these routine meetings and
9 for having us here.

10 As Paul mentioned, there has been a flurry of
11 activity on the Hill with regards to the oversight and
12 the protection of human research subjects, which has
13 in our view mainly focused on gene therapy and we have
14 been researching this issue of oversight protection
15 for the past year.

16 We have been looking at it from a more
17 broader view with regards to all human research and
18 that is the standpoint that -- where our bill comes
19 from.

20 Two important things that H.R. 3569, Mr.
21 Kucinich's bill, addresses is the current federal
22 regulations or the Common Rule and the oversight
23 mechanisms that are in place within the Federal
24 Government.

25 We looked at OPRR as the main model for

1 oversight and we found that while the mechanism in
2 place was appropriate, that there were many weaknesses
3 in terms of support, financial support, and limited
4 staff support as well, and so Mr. Kucinich wanted to
5 bring that out and allow adequate resources for OPRR
6 by making it an independent agency, and bringing it
7 out of the NIH and separating it from the Department
8 of Health and Human Services.

9 OPRR, we felt, still today, I understand they
10 are to move OPRR out into the Office of the Secretary,
11 we feel is still not an independent agency which, back
12 then, and we still do now, feel that it is a conflict
13 of mission. With it being in the NIH, OPRR is in --
14 is a regulator of human research and NIH is a funder
15 of human research, and we felt that that -- there was
16 a clash, perceived or real, there is a definite clash
17 there.

18 However, we are encouraged by the Department
19 of Health and Human Services to move it out of NIH and
20 we definitely support that move as a move in the right
21 direction.

22 Secondly, we wanted to address the issue of
23 oversight in other departments and other federal
24 agencies. We felt that there was inadequate oversight
25 in the 16 other departments that do human research and

1 there was a need to provide that oversight. That is
2 excluding the FDA. Of course, the FDA has its own
3 oversight mechanism which is very much in line with
4 OPRR's, but different nonetheless.

5 So those were the two main goals of our bill
6 and those were the two weaknesses that the bill
7 addresses.

8 H.R. 3569 brings accountability for
9 protecting human research by basically streamlining
10 the oversight mechanism into a structured manner and
11 it takes the authority from OPRR and brings it out
12 into an independent agency which we would rename the
13 Office for the Protection of Human Research Subjects.

14

15 We feel that this is something that is very
16 needed and something that has the support of many in
17 the bioethics community.

18 This umbrella agency would make accountable
19 all other federal agencies that do not have oversight
20 and that do have oversight, thus eliminating the
21 perceived or real conflict of mission.

22 We also believe that OPRR, as its function
23 within the Department of Health and Human Services,
24 should not be eliminated and that this bill would not
25 necessarily do that. It would not eliminate its

1 functionary role as a disseminator of information.

2 The Interagency Coordinating Committee created
3 by our bill is -- would be made up of the heads of all
4 the federal agencies that currently comply with the
5 Common Rule. It would allow the heads to make
6 recommendations on the Common Rule and have this
7 office report back to Congress on how the Common Rule
8 could be changed.

9 It would also give the authority to the
10 Director of this office to change the Common Rule and
11 make recommendations with respect to the exemptions of
12 the Common Rule.

13 Lastly it would -- it does not talk -- it
14 does not address IRBs or the make up of IRBs, which we
15 did not want to address in our bill. We were aware of
16 Mr. Waxman's legislation and we have been talking a
17 lot about that and felt that his legislation and that
18 of Representative DeGette's legislation were very --
19 was well addressed, the issue of IRBs, and so we
20 specifically did not want to talk or address the issue
21 of IRBs.

22 Our main goal here is to make a single
23 agency, an independent credible agency with enough
24 resources and accountability to protect human research
25 subjects, and we believe that this need has been

1 widely recognized.

2 And we look forward to the recommendations
3 that NBAC makes in the future and hope to work with
4 you in any way we can on the legislative proposals
5 that we have.

6 Thank you.

7 DR. SHAPIRO: Thank you. And thank you very
8 much. Let me thank both of you again for both your
9 presentations and for the effort in coming here.

10 Let me turn now to see if there are questions
11 from members of the Commission.

12 Yes, Alta?

13 DISCUSSION WITH COMMISSIONERS

14 PROF. CHARO: Thanks very much for coming.

15 Since Mr. Waxman is a cosponsor I guess I
16 will direct my questions both you, Ms. Al-Jadda and
17 Mr. Kim.

18 I wonder if you can clarify just a couple of
19 points in the bill as I was reading through it where I
20 was not sure I understood the intent behind the
21 language.

22 First, with regard to the range of human
23 beings who would be protected, the bill begins under
24 2801(b)(1) by saying that "The Director of this new
25 office will establish criteria to protect human

1 subjects..." and then it goes on to say "...in
2 research conducted, supported or otherwise subject to
3 regulation by the Federal Government."

4 I was not sure if you were intending through
5 this to simply mimic the current scope of mandatory
6 coverage of the regulations or if this was, in fact, a
7 suggestion that any area that was eligible for
8 regulation, for example, all human subjects research
9 via the commerce clause would be covered by virtue of
10 this bill so I was not sure if you were using this
11 bill to extend human subjects protection as far as our
12 resolution had suggested back in May of 1997 or not.

13 MS. AL-JADDA: Our intent was to extend its
14 coverage to all federally funded research in all
15 departments that comply with the Common Rule. So
16 private research would be excluded from this bill.

17 PROF. CHARO: Okay.

18 The second is, if I may and then I will stop
19 and yield the floor, Ms. Al-Jadda, you had suggested,
20 I think I heard, something about the enforcement
21 powers of this office but I am looking and I am not
22 seeing the section in which the enforcement powers are
23 spelled out exactly, and I just wondered if you could
24 help direct me because I am seeing a great deal in the
25 bill that is reminiscent of the way OPRR currently

1 operates.

2 It is very collaborative, through an
3 interagency coordinating committee, takes agreement
4 among the heads of various agencies, and what I was
5 not clear about was specifically the ability of this
6 office to determine regardless of the attitudes
7 expressed by people in other agencies to make certain
8 changes in the basic regulations and, second, to
9 enforce those changes as against other agencies or
10 even against individual IRBs.

11 I just was hoping you would clarify whether
12 it is here in the bill or if it is implicit in some
13 portion of the bill.

14 MS. AL-JADDA: Right. We have given
15 authority to the director to change -- to change the
16 Common Rule, the federal regulations. We did not
17 spell out how that would happen. It was something
18 that we have left out in terms of the procedures of
19 how it would be changed in terms of, you know, putting
20 it into the Federal Register or receiving comments on
21 it.

22 PROF. CHARO: If I can clarify. I would
23 presume that the Administrative Procedure Act would be
24 the basic --

25 MS. AL-JADDA: Right.

1 PROF. CHARO: -- governing statute with
2 regard to how you actually change the regulation. It
3 was not clear to me whether or not one would need the
4 active support of all or a majority of the members of
5 the Interagency Coordinating Committee or if this is
6 something that could be done unilaterally by the
7 director of the office --

8 MS. AL-JADDA: Right.

9 PROF. CHARO: -- where the coordinating
10 committee is simply -- it is politicked to get their
11 approval but it is not necessary.

12 MS. AL-JADDA: Right. That is correct. It
13 is not necessary to get their approval but they would
14 be giving recommendations to that.

15 PROF. CHARO: And in terms of enforcing
16 against other agencies, it would have that authority.

17 MS. AL-JADDA: Yes.

18 DR. SHAPIRO: Thank you.

19 Tom?

20 Excuse me. Diane, you were first. I
21 apologize.

22 Tom, you will have to wait a second.

23 Diane?

24 DR. SCOTT-JONES: Thank you both for coming.

25

1 I have a question for Mr. Kim. You mentioned
2 in your presentation to us that you are especially
3 interested in the special protections related to
4 children, and I was wondering if you could say a
5 little bit more about that and, in particular, of the
6 current Common Rule, the special subpart on children
7 has not been adopted by all the agencies that support
8 or conduct research with children. So could you say
9 more about your thinking about special protections
10 needed for children?

11 MR. KIM: You have put your finger exactly on
12 the -- one of the two sources of concern that we had
13 regarding the subpart that even under federal
14 funding was not a universal -- a question of universal
15 application -- and obviously that is something we
16 would like to see, but also to revisit them and to
17 hope that if there have been changes in clinical
18 practices or changes in standards that they might be
19 reflected in revisions to the subpart as appropriate.
20 And, hopefully, that will be a subject that the
21 Commission could work its way towards addressing in
22 this report.

23 But the second source of our concern was that
24 we were -- the premise for our adoption in the FDA
25 Reform Act of '97 of the pediatric drug provision,

1 which encourages this research and encourages sponsors
2 to conduct it, and then in exchange they get
3 exclusivity, was that there be more research involving
4 children.

5 And if we were putting a spur in place to
6 this field of research, our hope was that the
7 protections were in place and were at least adequate
8 and reflected current practices.

9 Not having that assurance and not being aware
10 of whether or not there is an activity within the
11 Federal Government or outside in terms of specialty
12 societies, the American Academy or others, we felt
13 that this would be an appropriate venue or an
14 appropriate way to address it in the whole context of
15 human subject protections writ large and that some
16 action would be taken in a timely manner.

17 We do not have a sense as yet as to precisely
18 how much research is being conducted by the companies.

19 We are just hearing back from the FDA as to the
20 number of submissions they are receiving from
21 companies to, you know, get the six months exclusivity
22 in exchange for the additional approved indication for
23 children, but our sense is that there is a great deal
24 of activity and our hope is that we could work with
25 bodies on the outside as well as the Commission in

1 developing and understanding what needs to be done.

2 DR. SHAPIRO: Diane?

3 DR. SCOTT-JONES: I would like, also, to ask
4 you what your thinking is on research with adolescents
5 as distinct from children who are younger than the
6 teenage years. Right now the regulations on children
7 apply to any person who is a minor and there has been
8 quite a lot of discussion over the last few years
9 about whether adolescents should be treated
10 differently from children and yet differently from
11 adults as well.

12 So have you given any thought to that?

13 MR. KIM: We have not but we are hoping other
14 folks are. In fact, that is precisely the kind of
15 change in practice and change in current thinking that
16 we hope would be reflected in any changes to the
17 subpart. We would not have any basis and expertise or
18 experience to be able to make any recommendations, but
19 hope that this will flow upwards and we will be able
20 to take advantage of your work on that area.

21 I am not aware of any consensus as far as the
22 fields or the specialties are with respect to the
23 status of adolescence but, hopefully, that is
24 something you can do for us.

25 DR. SHAPIRO: I think this point Mr. Kim was

1 just making, namely we create a spur out there to
2 include more children in medical experiments, is quite
3 real. I do not know what the numbers are either but
4 many researchers are talking to me about how they have
5 to put together their panels in different ways and so
6 on. So I think this is really a very important point
7 for us to come back to at some point.

8 But, Tom, you had a question?

9 DR. MURRAY: Thank you, Harold.

10 I want to thank Ms. Al-Jadda for coming. It
11 is great to see that Representative Kucinich of
12 Cleveland is weighing in on this. I have been away
13 for about a year now but still regard it as a very
14 important place for us.

15 I am going to direct my question primarily to
16 Mr. Kim.

17 I thought you gave an exceptionally incisive
18 account of the key issues. I think I certainly have
19 come to feel that human subjects research is under
20 renewed challenge, the ethics of human subjects
21 research. IRBs are overwhelmed and underfunded and
22 undervalued within institutions.

23 Complex financing, private financing
24 arrangements are becoming more the rule than the
25 exception with all sorts of potential, both individual

1 and institutional possible conflicts of interest.

2 Something must be done to ensure the safety
3 and protection of human subjects and to ensure public
4 confidence in the research enterprise.

5 Would you be open to more -- to call them
6 radical is to maybe over emphasize it, but to sort of
7 broader reconceptualizations of how to enhance the
8 protections for human subjects such as, for example,
9 as some other nations have done. Ensure that the
10 committees that review research are more independent
11 of the institutions under which the research takes
12 place and increasing the number of lay people, of
13 average citizens, looking over the research subjects.

14 Do you think there would be an openness to
15 that sort of consideration should NBAC recommend it?

16 MR. KIM: Those are precisely the questions
17 that we have in mind when we think about not only IRB
18 workload and administration, but also composition and
19 membership. Those are very important questions in our
20 minds and we recognize that the academic research
21 community will argue back, and appropriately so, that
22 this is an additional responsibility taken on
23 voluntarily by participants, that it is difficult to
24 incentivize participation, and the workload itself is
25 so extreme that it can take away from other essential

1 responsibilities.

2 But at the same time I do not think there is
3 any aversion to some open thinking about this topic
4 precisely because opening up of participation on IRBs
5 to the lay public -- maybe by changing the
6 specifications in the Common Rule, or requiring
7 different standards -- that would be responsive to
8 different forms of research we are also very open to.

9 And recognizing that there is a diversity of research
10 involved and recognizing there is a diversity of
11 research settings.

12 And on the final point you mentioned the
13 complexed financing. I just wanted to add that the
14 for-profit IRBs was a subject addressed by the GAO. I
15 think it is not very clear to us precisely how that is
16 influencing, if at all, the conduct of review by IRBs,
17 what sort of participation, what sort of uptake in
18 terms of research being evaluated by these kinds of
19 IRBs is taking place depending on source of funding.

20 We are very interested in getting to those
21 questions and there is a great deal of fact finding
22 that has yet to be done and we will have to perhaps
23 seek that from either the administrative agencies or
24 from the investigative bodies like GAO.

25 DR. MURRAY: Thank you.

1 DR. SHAPIRO: Steve?

2 MR. HOLTZMAN: Thank you to both of you.

3 This is directed to Mr. Kim.

4 With respect to the applicable -- broadening
5 the applicability and scope of the Common Rule, as the
6 previous speakers indicated, there is really two ways
7 one thinks about broadening the scope.

8 The first is to extend it to research which
9 is not currently covered because of the funding source
10 or -- not just that but because most of the private
11 research, if it goes through the FDA, is covered that
12 way regardless of the funding source, but rather
13 because broadening the scope of what is considered
14 human subjects research.

15 You did not have that in your list. I
16 wondered if it was something that was also on your
17 list.

18 And then the second question, and it ties to
19 what we were just talking about, is we imagine -- so
20 to speak, what are the sources of harm that are
21 arising? They can arise from activities which are, in
22 fact, currently covered by the scope but it is not
23 being appropriately done.

24 Second would be, it should be covered because
25 -- and it is, in fact, not being covered because of

1 the funding source.

2 And the third is because it is not being
3 considered human subjects research.

4 Do you have a sense right now of where in
5 those three is the major problem or is it a matter of
6 still not having the facts?

7 MR. KIM: I do not mean to abdicate
8 responsibility by saying we just do not have the
9 facts, but the appeal of the simple is to cut the pie
10 along the lines of funding source and saying, well,
11 this research simply falls out because it is not
12 federally funded or it is not at federally funded
13 institutions. For us, the appeal of extending the
14 rule -- the Common Rule and the protections in that
15 manner was almost intuitive at this point, and that is
16 the appeal there.

17 The types of research which are not covered
18 or which are not protected is also a question of great
19 interest to us, and we do not have the facts but it is
20 in a way a function of this -- the other way that you
21 cut scope and who is -- who does not apply.

22 We have heard the arguments that there are
23 significant burdens attendant to trying to expand the
24 scope of protections to privately funded research, and
25 part of that debate has already taken place in the

1 context of privacy.

2 What we are very interested in trying to
3 obtain and trying to ascertain are precisely what
4 kinds of research currently are not protected and
5 currently fall outside of the Common Rule because of
6 its private funding. If it is going to the FDA under
7 an IND then clearly it is captured. If it is
8 conducted at a federally funded academic medical -- it
9 is covered.

10 What we do not understand and the extent of
11 our knowledge really reaches only to things like *in*
12 *vitro* fertilization, perhaps. What other research is
13 being conducted that does not fall under the
14 protections? We do not have a good sense of that. It
15 may be that it falls below the threshold of minimal
16 risk and, therefore, you know, would be exempted. But
17 we are very interested in trying to get that
18 information and we are not certain how the best way to
19 go about that is.

20 We anticipate that there will be claims that
21 confidentiality or trade secrecy might attend to
22 disclosing that kind of information, but I think in
23 the interest of moving this debate forward there has
24 to be a full disclosure by research funders, whether
25 they be private or public, as to what they are doing.

1 We do not have an answer to that and I think that is
2 why we have not discussed raising or broadening the
3 protections in that manner.

4 DR. SHAPIRO: Okay. I will take the last
5 question from Larry.

6 DR. MIIKE: Am I correct in assuming that the
7 focus of the concerns in the Congress are primarily in
8 the clinical care and physical harm area and not so
9 much in health services research, public health
10 research and survey research?

11 MR. KIM: I think that is a fair statement if
12 only because it is what we are familiar with and have
13 a body of experience to work from.

14 More often than not an anecdote can have a
15 very powerful effect on our thinking, and many of the
16 anecdotes in many of the unfortunate incidents in
17 human subjects research are those which involve
18 clinical research and so that is I think the main
19 spring for our concerns.

20 But part of the process of education on the
21 Hill will certainly be information that you can share
22 with us and findings that you will have regarding
23 other fields of research and where there might be
24 potential abuses and the need for protections. Things
25 that we probably have not even gone into as far as

1 thinking is concerned.

2 DR. SHAPIRO: Thank you very much.

3 Well, first of all, I really hope that you
4 will convey to Congressman Waxman and Kucinich our
5 appreciation for the fact that both of you are here.
6 More importantly, for their interest in this area,
7 which is of great interest to us.

8 We began this project in the overview of
9 human subjects protection formally about a year ago
10 and, as you know and as you indicated, in our reports
11 we have taken on certain aspects of this now. We are
12 now in the midst of our comprehensive report.

13 We would hope you will tell both Congressman
14 Waxman and Kucinich that we would be delighted to be
15 helpful in any way as we go ahead. We would certainly
16 like to participate in hearings if and when those --
17 it is decided that those are appropriate and help out
18 really in any way that we can to move us to perhaps a
19 better spot than we are right now.

20 So, once again, thank you both very much for
21 coming. I am aware it is a little outside of where
22 you normally are sitting. It is a little bit of a
23 ride up from D.C. here and we appreciate your efforts
24 in coming.

25 Members of the Commission, unless there is

1 any other business we will adjourn.

2 Thank you. We are adjourned.

3 (Whereupon, the proceedings were adjourned at
4 2:43 p.m.)

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