37th MEETING

NATIONAL BIOETHICS ADVISORY COMMISSION

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I N D E X

P R O C E E D I N G S

OPENING REMARKS

DR. SHAPIRO: First of all, I would like to welcome everyone to today's meeting.

To my fellow commissioners, I think we have set a new record, that is in our second day meetings, which are always scheduled to start at 8:00, we have never started at 8:15. We always start at 8:20, 8:30. Today is a kind of new record. We have got a few laggards who are not here yet.

(Laughter.)

DR. MESLIN: You know who you are.

(Laughter.)

DR. SHAPIRO: That is right, and you know who you are but we are going to get started anyway because we have a number of guests here this morning and we are going to be focusing, as you will hear in a moment, on a subject, which is really quite critical and may be one of the more central parts of our so-called comprehensive project, the overview of the oversight regulatory system regarding oversight for

human subjects protection and so on.

As I mentioned yesterday, that was the issue of what we mean by research, the various kinds of research and how the regulatory system deals with them.

But let me turn first to Marjorie Speers, who is, of course, going to be the key staff person here in mobilizing ourselves for this to give you an overview of the work to date and to give you a framework for this morning's discussions.

Marjorie?

ETHICAL AND POLICY ISSUES IN THE OVERSIGHT OF HUMAN SUBJECTS

MARJORIE A. SPEERS, Ph.D.

DR. SPEERS: Thank you.

I want to refer to two documents that are in your briefing book. One is in section 3A, which is the update that I provided to you on the work of the staff on this project since the last meeting of the commission and I am not going to go over the update report in any detail with you. I do want to just make

two statements about that report.

One is that the federal survey is underway. We met with the federal agencies on December 13th in a meeting that Rachel Levinson had called together and hosted to bring the federal agencies together. We walked through the draft survey that we had at that time and got numerous comments from the federal agencies.

It was actually quite gratifying in the sense that the federal agencies seemed to be quite interested in the survey and added several questions to that survey so that the revised draft that went out, I think, is a survey that they feel that they can be responsive to and the deadline for receiving their responses is February 15th.

There is also in the update the mention of the possibility of NBAC conducting several town meetings in connection with the OPRR/FDA regional workshops. The first one of those OPRR/FDA workshops occurs in February in Houston. We have asked you in the update if you as a commissioner, are interested in

attending any of these workshops. We would really like to know of your interest.

It would be valuable, I think, to have at least one or two commissioners attend so if anyone is interested, particularly in the Houston workshop, please let us know as soon as possible.

Okay. Good.

DR. SHAPIRO: Could I just interrupt? Could I say a word about that? I really do want to encourage commissioners to look at the dates of these and the location to see if you could possibly make one of them, perhaps more than one but at least one. It really would be extremely helpful.

These will be very, very informative to all of us who manage to attend and so I hope that you will find time in your busy schedule and try to pick one which is perhaps geographically closest or the date is suitable for you and just let Marjorie or Eric know which one you would like to be at and they can make the other arrangements.

DR. SPEERS: Thank you.

Okay. Now I would actually like to turn your attention to Tab 3B. This is the proposed work plan for the project. This was an attachment that was given to you, I think, as you arrived here at the hotel so it may not be in Tab 3B but in one of the -- it is in the pink handouts that you received.

Following the December meeting, we took the outline that we had presented to you with the series of questions that we would address and formulated those questions into common groups of issues and then further into tasks and based on those tasks developed the work plan that is before you.

I just want to quickly go through this work plan and then ask you to provide comments to me or to Eric. I have suggested that you provide comments to us by January 26th. Comments should be -- what we are most interested in would be comments in the form of do we have the appropriate types of tasks outlined here. In addition to that would be names of individuals who you think would be appropriate to testify or individuals who could provide background papers, you

know, any other type of information that will help inform us on the various issues.

The work plan, like the outline, is divided into three broad categories. The first one I have labeled and it may not be the best label for it but it is the federal oversight of human research. What I am trying to capture in this category is for us to look at what the appropriate structure and system is for human subjects protection looking -- and we will be over the next few months -- looking at various regulatory models, perhaps even looking outside of regulatory models.

We use the word in here "common rule." You might think of that simply as a shorthand to capture when we talk about a regulatory system but we really want you to think and have the commission think outside of simply the “common rule.”

The second broad category is the common rule in practice. After we have considered some of the conceptual issues, we would then move to some of the practical issues around what our current regulatory

structure is and how that operates.

And then the third one is to look at our current IRB system.

This work plan covers essentially a 13 month period. We have taken the commission meetings and projected out from January 2000 to January 2001 essentially and have tried to move through the various topics as we would cover them over the next 12 months.

To make the work plan a little bit easier to review, at the very end of the work plan is the agenda where you can see the various topics and how we would propose to cover them. It is based on a model of generally having three or four meetings and then a point where you would discuss the issues. We could bring -- hopefully, bring several issues to closure and look at recommendations for those issues.

I think about the data collection, if you will, for this project sort of occurring in two ways or there being two separate processes, separate but related. One where there will be papers, background

papers, that will be written. Some of them will be followed by testimony. Some of them may just come forward to the commission for your discussion.

In addition to papers we want to use the format of town meetings or workshops as a way to have additional information presented to the commissioners and then we will have testimony at the various meetings.

We are starting, if you will, at the top, which was Harold's words at our last meeting, with two issues. One is the definition of research, which we started yesterday with Bob Levine's testimony.

The -- our plan is to -- is to discuss -- to move from Bob's testimony to discuss several areas in health, public health, and then eventually with health services, two areas in health that have problems implementing the current definition of research, and then to move from health to the social sciences and to look at some of the issues that they have with the definition of research and then probably in two meetings to come back for the commission to

then discuss what they would like to recommend regarding the definition of research.

The other area that we are dealing simultaneously with initially is looking at regulatory structure.

Remember the background that you already have and that you have heard from John Fletcher and Charles McCarthy and others regarding -- it was under the general topic of the placement of OPRR but when you look at those background papers and the testimony that they provided it certainly helps to inform us on this decision as well.

So we will start there and then with those two issues try to bring them to some resolution probably in the spring and then through this outline.

DR. SHAPIRO: Thank you.

Are there any questions?

Alex?

PROF. CAPRON: On the last point that you raised, I could not tell if your suggestion was that we were going to mine the McCarthy, Fletcher and -- I

am sorry, the third one --

DR. SPEERS: Gunsalus.

DR. SHAPIRO: Gunsalus.

PROF. CAPRON: -- Gunsalus' papers for other points or are we -- do we still have the OPRR "placement" issue on the table in your view?

DR. SPEERS: In my view we want to mine those papers for the other issues. I did not see that the primary purpose of using those papers now was to address the issue of the placement of OPRR in the sense that a decision has been made about moving OPRR from NIH to HHS.

I think what is still on the table or what should -- what could still be on the table is the general issue of whether as part of the federal structure there should be an overall office -- if you will, an office that provides oversight to all the federal agencies that would be separate from OPRR. I see that issue as one of the issues that is mentioned in those papers that has not been addressed.

As you look at this outline, you will see

remnants of what was discussed in some of those papers in the sessions that are coming up.

The Gunsalus' paper is a good example of one that discusses the definition of research, of human subjects, of covering nonfederally funded research. So those kinds of issues I still see as being on the table.

I mention those papers in one sense that we do not want to lose sight, and I particularly having joined the staff only recently, do not want to lose sight of the history of what the commission has already heard and debated on this topic of the human subjects protection system.

PROF. CAPRON: Well, I raise it because, of course, the reason we commissioned the papers was to have one paper that was going to say move OPRR and another one that was going to say do not move OPRR. We got two papers that said move OPRR. One said get it out of NIH. The other one said get it out of HHS.

We had some preliminary discussions with the authors. I, for one, thought that the better argument

lay with John Fletcher's position.

I must say Charlie McCarthy's paper was a wonderful paper in terms both of the thought that went into it and the information that he was able to convey. It is one of those great things about sort of personal historical memory of many of the battles that were there.

The Gunsalus' paper was originally written at the suggestion of David Cox and it was very much on this issue of the possible interest that the private sector would have in having an overall structure. And I think the thought was that that was going to be more likely if you had something that was not departmental because the notion of supervising private research out of the Department of Health and Human Services as opposed to out of a separate agency seemed to make more sense.

Now, of course, FDA is part of HHS and so, you know, it is not inconsistent but the notion of reaching nonfederally funded research seemed to make some sense as part of the move and I assume that that

issue is still on the table.

Her paper really did not provide that. It was a very interesting paper but it was not what David had in mind and I raise it to ask whether given the fact that we now have some months that we will be working on this project if it would make sense not to look in academia but to look in the private sector for someone who would have the ability to -- perhaps as a more reportorial function -- in a way explore whether there is, in at least a segment of the private industry, a sense that Americans generally, and people who become subjects, but also their own interests would or would not be served.

David was of the view that there would be a lot of support. A lot of people that were doing research that is not federally funded would like to see it conducted according to the same standards, et cetera, et cetera. They may have had some issues about it and those issues were going to be explored but he thought there would be interest.

I do not know whether that is the case or not

having read that paper because it really did not, in the end, address that at all so I want to just put on the table the thought that we still could use that and I hope that the underlying issue has not been lost by the fact that the Secretary has decided to move OPRR.

Many of the conflict issues that were raised, it seems to me, still arise. What the move does is make it clear that CDC and other agencies that do research within HHS no longer can say, well, that is sort of an NIH operation and we do not really like reporting to it or having it supervising us. It is inappropriate.

Well, now it is in the Secretary's office or will be.

DR. SHAPIRO: We have got a number of people who want to speak.

Eric?

DR. CASSELL: I just want to say a commission self-congratulatory thing. I think the scope of the investigation in the human subjects issue is large and very, very good. From the conversations I have had

with the IRB people that I know, just refocusing was not the way to go at it and I think this is wonderful.

DR. SHAPIRO: Rhetaugh?

DR. DUMAS: I am very -- not having had time to look at this very closely, it seems to cover all of the important areas and issues that come to my mind and it is comprehensive and I am pleased with it.

DR. SHAPIRO: Thank you.

Bernie?

DR. LO: I also think this is a wonderful overview and wanted to thank and congratulate Marjorie for putting this together.

I have a couple of concerns. One is sort of the flip side of what Eric and Rhetaugh just said. This is beautifully comprehensive. We are in a very tight schedule. I am just concerned that there is not a whole lot of room for slack or slippage here and I am just wondering if we really are going to be able to do all this in our time frame.

I know there is a -- as I read it through, it struck me there is a lot of very good ideas of holding

hearings and commissioning papers on particular topics. I am just concerned that if something slips, we may not end up with enough time to deliberate and get the report together.

My second thought, again tying into sort of looking towards the future and our limited time frame, is it seems to me there are two approaches to this. One is more or less a regulatory approach. Sort of what needs to be changed and modified in the actual regulations. It seems to me the other is a more voluntary approach. What can we recommend for IRB's and investigators to do, whether or not the regulations change?

I guess my own view, given our finite life span, is that we may want to spend more time on the latter thinking that that would outlive whatever the span of this sort of commission might be.

I think -- I say that not just because of any kind of pragmatic concerns due to the sort of impact we will have but also my sense that a lot of IRB members and IRB chairs have really understood that

there is a lot of public concern about what they are doing. I think this has filtered down to researchers, you know, at least to the extent that they know that colleagues at other universities have had to close down their shop.

So I think there is an audience out there that would be willing to listen to a well thought out report that encourages them to go out and either do things differently or think through things differently.

So I just offer that as a way of addressing what I am concerned about the potential problems nof trying to get everything done on schedule.

DR. SHAPIRO: If I could say a word about that, Bernie. I think those are good suggestions and I do not doubt that the report is going to have a lot of the latter but I do not think we need to divide that up right now. We will wait and see how we go and how it progresses and so on.

Tom?

DR. MURRAY: Thanks, Marjorie. This is very

impressive.

I am not sure how one evaluates such a work plan for its comprehensiveness except by putting questions to it and I have been doing that pretty -- as systematically as I can and every time I have a question virtually the answer is here. I mean, you are going to deal with it.

Two things that I would like to ask, and they may well be just deeper down in the level of detail and may already be included. One is some information about different -- other nations' experience with their ways of protecting research subjects, and I am most familiar with the situation in New Zealand. I have mentioned it before. They have gone to a system where the research ethics committees have a majority of lay people on them, not institutionally affiliated people. We will cover that in membership as a general issue but it would be helpful to have some information about the experience of other nations.

The second is I saw no mention of compensation for injury in research. Is that regarded

as a settled issue or a separate issue?

DR. SPEERS: With regard to the first issue, it is in the outline. It is imbedded under 1D, alternatives to the current human subjects protection system on page 2. What we plan to do there is to look at several of the foreign models.

There are -- on the issue of compensation, there are two issues. Compensation and confidentiality. Two issues that were brought up at the December meeting as I went back through the transcript. I saw both of them in there that are not in this outline per se. Those topics have not been dropped. It is an issue of trying to figure out where they will fit in here and we will place them appropriately as the time comes.

Particularly -- if I go to confidentiality for a second, particularly with that issue we will want to follow what is happening with respect to privacy and confidentiality with the HHS recommendations and then as we follow that process decide where it is appropriate to fit it in here.

Compensation has been actually mentioned twice by commissioners and it will not be ignored. It will go into the outline.

While I have the floor I wanted to say one other thing. Bernie, I thought the question you were going to ask me, and I had it in my notes and then did not say it, the question I thought you were going to ask or the comment you would raise would be you have not given education enough attention.

(Simultaneous discussion.)

DR. SPEERS: Okay. It is both of you. Both of you. Okay.

And what I wanted to say is that what I have not done on any of these items is given any weighting as to which ones are particularly more important than others or which ones we may have stronger recommendations on than others.

One of the reasons for placing education later in the outline is that I think that as you hear from various researchers and investigators and IRBs, the case for education and training on various levels

is going to speak very loudly and so I think it is appropriate to consider it towards the end after you have heard testimony, and we have a number of papers from various groups.

But I see it as -- if we were to weight these, it would have a higher weight than some of the other issues in the outline but there has been no weight assigned to any of these topics.

DR. SHAPIRO: Larry?

DR. MIIKE: Yes. I think maybe it is imbedded in this outline but what I do not see here is what are the main areas in which we are going to have our specific conclusions and recommendations? I think it has been a useful process in our last two reports to get on that early and I note some of those things in the agenda but it is now given in piecemeal fashion. I would rather see an outline on a document that says these are the major areas in which we have to make some conclusions and the recommendations that would follow from those conclusions.

PROF. CHARO: Hand up.

DR. SHAPIRO: Just a second, Alta.

Did you want to make any comment on that?

DR. SPEERS: Yes. I think that the next -- the next step is, as you have done for other reports, is for us to begin to look at -- to shape what a report would look like. Excuse me, what the chapters in the report would look like. Areas where you are going to want to make recommendations and that, I think, is something that we could commit to having for the next commission meeting.

DR. SHAPIRO: Thank you.

Alta, you sound better today so you are going to have to wait till Jim speaks before --

(Laughter.)

DR. SHAPIRO: Jim?

DR. CHILDRESS: Alta, I will be brief.

I would join the chorus of praise for what has been presented here and for the work plan. I would also want to concur with Larry that I think it would be very useful for us to begin to formulate the kinds of reports that are critical in terms of

possible recommendations really to give some shape and structure to our thought processes along the way.

I guess in terms of the question about feasibility given our time frame, it would be -- I am assuming that, first of all, we do not have budgetary problems right now so we really can commission all these papers.

Second, that the process is already well underway for getting the papers done because if we could get those in a timely fashion then I think that will help deal with some of Bernie's concerns about whether this really is do-able in the time frame.

DR. SHAPIRO: Thank you.

Alta, with the latest symptom I just heard we will have to recognize you quickly.

(Laughter.)

PROF. CHARO: It is not the cough, it is the mono that is the problem.

DR. SHAPIRO: I see.

PROF. CHARO: First, my apologies because the connection today is different and it is very hard to

hear you so I hope I did not miss this.

Marjorie, I wonder if we can keep track of a very small topic that may come up under accreditation possibilities and that is rather -- not only accreditation of IRB members or of IRBs but accreditation of actual investigators, which is a suggestion I have heard raised.

DR. SPEERS: Okay. Yes.

PROF. CHARO: It is not a big deal. Just if we can keep track of it in the course of the writing.

DR. SHAPIRO: Okay. Thank you.

Any other comments right now before we -- Marjorie, is there anything else you would like to say right now?

All right. Let's proceed on then with our agenda and again, Marjorie, thank you very much for the very comprehensive plan you have provided for us.

We will now move to a part of our sessions where we have a series of very important speakers here this morning dealing with definition of research issues we began discussing yesterday with Professor

Levine. We will discuss it today. Of course, there is a second panel later on the -- really proceeding on different aspects of that regarding the establishment and implementation of federal regulations, their interpretation and perspectives from various agencies, and so on.

As Marjorie indicated a moment ago, we are trying to deal with public health, public services kinds of issues today with some of the testimony we are going to hear and the next time we will be more focused on some of the issues as they come up in some of the social sciences.

But our first speaker today is Dr. Dixie Snider from the Center for Disease Control and Prevention.

Dr. Snider, I want to thank you very much for agreeing to speak to us today. Welcome to our meeting. I turn the meeting over to you.

PANEL I: THE DEFINITION OF RESEARCH: PROBLEMS AND ISSUES

DIXIE E. SNIDER, M.D., M.P.H.,

CENTERS FOR DISEASE CONTROL AND PREVENTION

DR. SNIDER: Thank you very much, Dr. Shapiro. It is my pleasure to be here and to speak to you about the definition of research in the context of public health.

My name is Dixie Snider. I am the Associate Director for Science and among the many things I am responsible for at CDC is the protection of human subjects, the operations of the IRBs, scientific misconduct, and so forth.

CDC, as hopefully most of you know, is an operating division of the Department of Health and Human Services. Its mission is to promote health and quality of life by preventing and controlling disease, injury and disability.

The first thing I want to emphasize is that CDC is first and foremost a public health agency. That is, it conducts those activities that are directed to the maintenance and improvement of the health of the entire population, which is one of many definitions of public health.

And that is that CDC is relatively more focused on society or the population as patient than the individual as patient. We are also relatively more focused on the prevention of a disease, injury or disability than on its cure.

Now in accomplishing its mission CDC has used a common sense data driven approach. We call it the public health approach and it really responds to five questions.

First of all, what is the nature and magnitude of a particular problem because we are an agency that responds to problems. To answer the question about the nature and magnitude of the problem, we may use public health surveillance data. For example, information from case reports that are mandated by law to be submitted to health departments. Or we may use a variety of other data sources such as medical or laboratory records, vital statistics or surveys. Or we may conduct outbreak investigations such as was done this summer in New York city when West Nile Fever made its first known appearance in the

west -- in North America.

The second question then is what is the cause of the problem? And answering that question may require, for instance, looking for etiologic agents such as micro-organisms or toxicants or looking for risk factors such as certain behaviors.

The third question is what might work to prevent the problem? By drawing upon what we have learned about the problem and its causes and by knowing what has worked in the past to prevent similar problems, we identify interventions which might prevent the particular problem we are facing now and in the future.

Then we ask how can we and should we implement a prevention and control strategy, and this step involves devising and implementing usually several interventions at one time rather than just one. So that they are likely to work in a particular place and situation.

So it may require educating people about using seat belts and passing a law on seat belts or it

may require establishing a prevention and control program which has a broad range of activities like an AIDS prevention and control program.

The last question, of course, is how well did the strategy work and, using a variety of methods, we conduct ongoing evaluation activities to determine whether the intervention has had the desired effect and make adjustments if it has not.

Now although CDC's problem oriented approach has served the agency well in accomplishing its mission, our approach has presented some problems, I think, when it comes to the oversight of human subjects research. CDC conducts a variety of activities to accomplish its mission. As I said, public health surveillance, emergency responses, program evaluation, public health capacity building. We provide technical assistance and training. We provide funds and develop guidelines, develop policies, are involved in public health communications, and of course in research activities.

But when we address a public health problem,

all of these functional activities tend to run together to form a prevention and control program that is performed by the same people so the distinction between researchers and nonresearchers or a distinction between an activity that is research or nonresearch becomes somewhat difficult.

Furthermore, historically, and I have to be completely open about this, until the 1990's, I think the thinking within the department was that CDC rarely conducted research activities. Research was the province of NIH. With some obvious exceptions, such as experimental design projects, CDC did public health and NIH did research, period. We do not think like that anymore.

Furthermore, to address the broad spectrum of today's public health concerns, CDC has increasingly relied on a whole variety of disciplines to carry out its mission. So in addition to epidemiology, we have a whole variety of laboratory scientists, statisticians, engineers, behavioral scientists, social scientists, physician scientists, and many, many others. Each

discipline tends to have its own concept of what constitutes research and what constitutes public health practice.

In addition, the effective practice of public health today requires that CDC fund and collaborate with a broad range of partners. Traditionally we work with state and local health departments but today we would add community based organizations, academic institutions, volunteer groups, philanthropic foundations, labor unions, industry, HMO's and other health care provider groups and professional societies.

Some of these groups have a long history of conducting research and they have a well developed infrastructure for its oversight while others are unaccustomed to working in the research area. They lack an infrastructure to support institutional reviews and are relatively human subjects research naive, and this creates a number of problems, not just around the issue of definition, which I could talk about at a later date.

The point I have been trying to make, I think, is that the environment in which CDC conducts its research is quite different from the biomedical and clinical research model of academia or NIH and the model for which we believe at least the current regulations were written.

Of course, CDC is committed to protecting individuals who participate in all public health activities, whether they are research or nonresearch. In the conduct of public health research, we follow the Code of Federal Regulations, Title 45 Part 46, but the practice of public health poses some challenges in implementing 45 CFR 46. One of those challenges is defining research in the context of public health practice.

Now this difficulty in classifying public health activities as research or nonresearch can stem from traditionally held views about what constitutes public health practice or from the fact that 45 CFR 46 does not directly address many public health activities.

In addition, the statutory authority of state and local health departments to conduct public health activities using methods similar to those used by researchers, is not recognized in the regulations.

The regulations state, as you know, research is a systematic investigation, including research development, testing and evaluation designed to develop or contribute to generalizable knowledge.

Now obtaining and analyzing data are essential to the usual practice of public health and for many nonresearch public health activities, data are systematically collected and analyzed. So systematically collected is not a term that is very helpful in distinguishing for us research from nonresearch.

Scientific methodology may be used both in nonresearch and research activities so methods of analysis, for example, do not really distinguish research from nonresearch.

Because scientific principles and methodology can be applied to both nonresearch and research

activities, knowledge is generated or can be generated in both cases. The extent to which that knowledge is generalizable may not differ greatly in research and nonresearch.

I would point out that the issue of generalizability is often a subject of great debate in epidemiologic research so that research itself is not often very generalizable and then the question is generalizable to whom and at what point in time. Is it just today or for the future or is it just for this particular population?

A key word in the regulation's definition of research for the purpose of classifying public health activities is designed and, as best we can tell, the major difference between research and nonresearch lies in the primary intent of the activity. The primary intent of research is to generate or contribute to generalizable knowledge and the primary intent of nonresearch public health activities is to prevent or control disease or injury and improve health in a specific population at a particular point in time.

During that process, knowledge may be gained and in some cases that knowledge may be generalizable but the primary intent of the endeavor is to benefit the population from whom the information is gathered.

In other words, we believe there is a public health equivalent to the clinical practice of medicine and that public health practitioners have the responsibility to examine, diagnose and treat the populations they are responsible for just as clinicians examine, diagnose and treat their individual patients. Both do this generally outside the context of research and human subjects regulations.

Now making distinctions between research and nonresearch is particularly problematic for three public health activities. Surveillance, emergency responses and program evaluation.

Public health surveillance is the ongoing systematic collection, analysis and interpretation of outcome specific data closely integrated with the timely dissemination of these data to those

responsible for preventing and controlling disease or injury.

As I noted earlier, surveillance may constitute notifiable disease case reporting and is mandated by state law but increasingly a wide variety of methods are being used to collect public health surveillance data.

An emergency response is an activity undertaken in an urgent or emergency situation because of an identified or suspected imminent health threat to the population. The primary purpose of the activity is to document the existence and magnitude of a public health problem in the community and to implement appropriate measures to address the problem.

Program evaluation is the systematic application of scientific and statistical procedures for measuring program conceptualization, design, implementation and utility, making comparisons based on these measurements and the use of the resulting information to optimize program outcomes.

But while in the majority of cases these

things are nonresearch activities, some surveillance projects, emergency responses, and program evaluations are research involving human subjects. Therefore, each project must be reviewed on a case by case basis.

For example, an emergency response may have a research component if samples are stored for future use which are intended to generate generalizable knowledge or additional analyses are conducted beyond those needed to solve the immediate health problem. Or when investigational new drugs are used or drugs are used off label then the emergency response is almost always research.

Another example is provided by program evaluation efforts. CDC funds and provides technical support to all state health departments to conduct specific prevention programs. This funding typically encompasses program evaluation activities that local managers use to monitor program performance.

CDC may aggregate information from these local evaluations to evaluate the so-called national

program and guide technical support activities to grantees. Deciding when evaluations constitute research or nonresearch can be quite complicated.

For surveillance, emergency responses and program evaluation, the question of defining primary intent can be difficult, especially when there may be and often are, multiple objectives or multiple intents at multiple levels of government from local to state to national.

To help public health workers distinguish research from nonresearch activities in public health, Donna Stroup and I published an article in Public Health Reports in 1997. I shared this report with the commission. In addition, CDC, Marjorie Speers in particular, has worked with the Council of State and Territorial Epidemiologists to develop a policy on this issue. I have also shared this document with the commission.

But despite the availability of these guidelines, we continue to struggle with the interpretation and application of 45 CFR 46 in the

context of our public health mission.

As the commission reconsiders human subjects regulations and the definition of research, we would appreciate your keeping public health activities in mind and, in particular, we would ask you to explicitly consider including or excluding certain public health activities in the definition of research or in some other way clarifying the definition.

Although it might not ever be possible to draw that clear sharp line between research and nonresearch in public health, we would hope that the distinctions could be brought into sharper focus than they are now.

Thank you.

DISCUSSION WITH COMMISSIONERS

DR. SHAPIRO: Thank you for your thoughtful remarks and thank you also for the materials that you have provided us, the articles which you referred to just a few moments ago.

Let me now turn to questions from commissioners.

Bernie?

DR. LO: I want to thank you for your very helpful remarks and for the materials you gave us which were very well done.

I want to ask you to say a little bit more about the implications of your point that a lot of public health activities are really public health practice and not research in terms of the implications.

It is often said that the federal regulations sort of embody two major ideas, informed consent and review by IRBs, and I am trying to think through what would be problematic if certain public health practices were sort of considered research and, therefore, to fall under those sorts of regulations.

It seems to me consent would be difficult for alot of surveillance and program evaluation and I suppose that for something like emergency response having to go through independent review would preclude it being -- might preclude it being done in a timely fashion.

On the other hand, I know that public health as a field has traditionally paid tremendous attention to the protection of individuals being -- whose data -- on whom data is being collected and certainly confidentiality in the public health system, you know, is given tremendous importance and practices are very carefully crafted.

It struck me that it is almost like a model for how to pay attention to the idea of protecting confidentiality of sensitive data. So I am just wondering even though a lot of public health does not fall under the ambet or should not fall under the ambet of research for the very reasons you stated, do nonetheless some of the concepts that have evolved for ways to protect human subjects, do they find robust embodiment in public health practice and could that be used to illuminate how, for example, confidentiality might be protected in other ways?

I am just wondering, for example, in public health practice for something like surveillance where there may not be as timely -- a timely response may

not be as critical a factor as it is in emergency response, whether, for example, there is independent oversight of data bases to make sure the confidentiality is protected and things like that.

DR. SNIDER: Thank you for that question.

I think I will try to be as brief as I can in responding to it but the answer can be quite extensive and complex.

First of all, I want to make a distinction between whether public health should get informed consent and whether an activity should be classified as research and subjected to IRB review. For me they are two different issues.

I think there are a lot of contexts in which public health does get -- does inform people. At times, for example, with mandatory school immunizations you cannot really call it informed consent but there is a vaccine information sheet that providers are required by law to provide to the parents or to the recipient of the vaccine prior to their receiving the vaccine.

Of course, when I say there are mandatory laws, there are also philosophical and religious exemptions to vaccination so that in many public health contexts I think that we do inform people. In many public health contexts, even in emergency responses that are not research, we will be getting some kind of informed consent.

It may be oral if it is an emergency situation or it may be written and yet it is not a research activity but I think public health, in general, could do a better job in thinking through when it would be appropriate to obtain informed consent.

Another thing I think public health could do a better job of relates to the privacy and confidentiality issue because I do not think that -- well, most health entities could do a better job and it is the whole point of the privacy rules that are being put forward by the department in any law that we would like to see that have health entities, public health or health care entities, do a better job of

telling people what information they need and how they are going to use that information, who it is going to be shared with, how it is going to be protected and so forth.

Sort of like other health entities I think public health could do a better job in telling people what they are going to do with the information.

By and large, I think public health, given the voluminous data that it has collected over the years, has done a tremendous job in maintaining confidentiality.

Some of the implications of trying to get informed consent in certain circumstances are -- would be dramatic. I mean, for example, if a person who had infectious multidrug resistant tuberculosis and had to give consent for their name to be reported to the health department and chose to walk around communities such as Washington, D.C., without treatment and spreading multidrug resistant disease, it would be considered inappropriate and, in fact, in just about every jurisdiction the Commissioner of Health would

probably be relieved of duty and in some cases could probably be even fined or jailed for not carrying out their responsibilities, which gets me into another area.

And that is that -- you know, how do we consider a lot of these public health activities and the IRB process or at least the lay review process that someone was talking about earlier -- in which a legislature has directed the -- you know, its state government to carry out public health activities.

You know, is that a kind of IRB review if the whole legislature has to make decisions about carrying out certain activities or how should that count as society endorsing the legitimacy of a certain public health activity?

So I think there are a lot of complexities around these issues that I could go into even further but I do agree that public health could do a bit better in informing people about confidentiality issues and about what the purpose is of collecting certain data but I think at the same time there is a

lot of public health that it would be impossible to carry out properly if we had to get individual informed consent.

DR. SHAPIRO: Thank you very much.

Larry?

DR. MIIKE: Let me preface my remarks. My question really is what procedures you have established in CDC to help you decide to make these decisions.

What my preface is as follows: I agree with much of what you said that if you just substitute populations for patient, then you are doing the practice of public health as opposed to research but then I was puzzled by some of the things that you were mentioning, that you parsed out the definition of research and sure one particular piece of that may fit the research model but not the definition as a whole. It is not a little piece here and there so you can design something. It can be scientific methods, generalizable, et cetera. But the way that you explained it was you said, well, you know, you can

design a public health program but research is designed if you took the next step, et cetera.

And then you also mentioned something about parts of a research project may be collection of tissue samples for research in the future. Well, they do that in hospitals all the time in patient care and you have to have informed consent.

My basic question is essentially how much of this is the agency not being acutely aware that they are conducting some research and they are overreacting to the situation and being extra careful and trying to define things that even you agree may not be research but saying, well, we better put this under the purview of IRBs because we are worried they may be criticized.

DR. SNIDER: All right. Well, I think the increased sensitivity to these issues, education and awareness, all play a role. I think that many of CDC's investigators who come on board today are better informed about how to make these decisions as a result of the courses we put on, the CD-ROM course that we have, et cetera.

Our approach is that those who have to review the funding documents, those who review the protocols, who generally are associate directors for science in the various divisions and in the centers, institutes and offices, work very closely with us in the Office of the Associate Director for Science to write up these policies and develop the training courses. They are very much aware of the difficulty of making these distinctions.

In addition, we have the people in our procurements and grants office sensitized to alot of these issues who are able to look at applications and try to tease out the applications, whether an activity is a research activity or not.

But having said all of that, I think generally we tend to lean toward calling something research or at least reviewing it and making a determination at a fairly high level but even doing that I think in the end we find lots of projects where we -- whether it is Marjorie, whether it is me, whether it is Marjorie's replacement -- have a hard

time looking at 45 CFR 46 and knowing for certain whether it was the intent of the authors to classify the activity that we have in front of us as research or nonresearch.

DR. SHAPIRO: Thank you. I have quite a few commissioners who want to speak and we do have to call this part of our session to a close in approximately ten minutes so I would ask both people who have questions and a minimum response to keep that in mind.

Jim, you are next.

DR. CHILDRESS: Thanks for the illuminating comments today and also for the very helpful papers. At the end of your 1997 article you issue a call to the public health community and others to engage in a discussion of these issues. I just have two quick questions.

One is has that discussion occurred in various ways? And, second, what are the major tensions that you see in the competing positions? That is what sorts of alternative positions should we

be attuned to as we try to think about how to deal with public health and the issues like surveillance and so forth you raised?

DR. SNIDER: In answer to your first question, I think the engagement of the Council of State and Territorial Epidemiologists in producing that second document that you have has been the major response of the public health community.

Although I have to admit that in the past few months Jeff Kohn and some others who are members of the American Public Health Association and also members of the American College of Epidemiology have expressed an interest in trying to address more adequately the bioethical underpinnings, if you will, of public health because I think one of the problems we have in public health relates to the lack of a clearly articulated ethical framework for the conduct of public health. And that obviously has to do with a lot of public health activities in addition to research activities.

In response to your second question about

what are the particular sensitivities, I think one of the major sensitivities that we have gotten from the states -- I will call it a state's rights issue. It is around this issue of state laws.

If the state legislature is telling me to do this, how in the world, you know, can you all possibly be requiring us to have an IRB look at it when the legislature, the representatives of the people has already said do it? How can a group -- a small group of IRB people be in a position to say go or no go on this? So the state's rights issue, I think, has been a big one.

Another issue, I think, has to do with the -- with the emergency response situation or the program evaluation situation or the surveillance situation that begins as a nonresearch activity and then evolves into a research activity.

That is a challenge for all of us at the, you know, state, local and federal level because we may approve something that starts out and it is pretty clear to us that, no, this is not a research activity,

this is a regular public health practice activity, and then lo and behold we have the issue of IRB review and informed consent facing us because it has evolved.

A third thing I would say that has been a tremendous problem has been all the new entities that we are working with in public health. You work with community groups that represent commercial sex workers, that are advocates for drug treatment for i.v. drug abusers, work with a lot of organizations like that that do not have an infrastructure that supports human subjects review, and do not really have the connections in academia or with a school of public health. They are out there by themselves, you know, trying to accomplish something worthwhile in their communities.

We are putting a heavy burden on them and many times we have projects that may have 10, 20, 30, 100 of these different entities and we have to go through all these hoops with each "performance site" and many of them do not -- of course, they will not have multiple project assurances so we are getting

single project assurances from all these different entities and multiple IRB reviews in different locations by many people who do not understand the research process or informed consent process. It can be a nightmare.

DR. SHAPIRO: Thank you.

Alex?

PROF. CAPRON: Dixie, I appreciate your introducing this topic to us so well. It seemed to me that some of the problems that you talk about are ones which we hear in other sectors of activity which also feel they do not meet the sort of pharmacological clinical trials model that is closer to the heart of what goes on in the usual definition of research.

We hear it from surgeons and the fact that surgery often do not fit -- surgical innovations does not fit very well.

In terms of acting on official authorization, research that involves the military and soldiers being given experimental interventions which have been approved by people who act on public authority the

same kinds of issues arise.

Bernie raised for us sort of the functional approach. I mean, what is going on? What are the activities? Are they well handled? Do you get consent when you need it or do you operate with good confidentiality protections?

Your paper puts the emphasis instead on intent and I think from a philosophical point of view that is an interesting way to proceed and I hope we give some thought to that. You do not put it this way but I would say that the reason we separate out research and do have these additional procedures and the IRB review and so forth is a recognition that there is in the step to research the potential for a conflict of interest in the professional engaging in the intervention.

And most classically, the physician who becomes a researcher for her patient or his patient, is a person who now has some objective other than the one which the patient would otherwise expect which is solely the patient's interest.

The complicating factor here is that inherent, it seems to me, in what you are saying in a lot of public health activity is already the sense that, I as an individual, am being looked at and surveyed or engaged in some program evaluation activity or something for the purpose of developing information directly of benefit to others.

I mean, the reason for doing that is to see what is the pattern of this disease? Do we have a way of containing it and all the things that you went through? So already inherent in your activity is something which has that other focus.

The major problem I hope that we can think some more about, and I would like your comment on, but I realize we are not going to have a lot of time to discuss it today, is if we did take the intent route and say, is the activity designed for the purpose of a public health practice or for the purpose of developing generalizable knowledge, is how practical is that as a standard to implement?

I mean, any time you deal with intent, you

are dealing with something which in certain ways is the hardest thing to have a handle on. I mean, well, I intended to do this. Well, how do I know that?

And so my question is, are there ways short of engaging in a full IRB review when that is not timely or a full process of consent when legislation dispenses with consent of imagining a statement of design or something which would be made early in a process subject to revision, as you say as the process goes on, which at least as kind of a public filing as it were -- I mean, I -- so that -- so that we are not, after the fact asking someone, well, what did you intend but right from the beginning I could say the intent of this is X, Y, Z, and it comes within standard public health practice or the intent is to develop something new, we are dealing with a new area, as a way of recognizing the attractiveness of your underlying philosophical idea and giving it some practical reality. Is there any practical way of doing that?

DR. SNIDER: Well, we have been doing it and

we -- to be perfectly honest with you, we do find it problematic. Mainly, though, because it is a lot of hard work. Not because we cannot get at the answer. We have to keep talking and pumping and pumping people for the information about why they are doing it and be skeptical.

I want you all to understand that I am not here to try to get public health off the hook of anything.

PROF. CAPRON: You have not given that impression.

DR. SNIDER: I want -- what I am -- my main message is, think about public health as one of the models when you think about the definition of research and tell us what to include and, you know, what we can exclude to the extent that you possibly can.

I certainly agree with you that public health, you know, is -- gives this natural conflict between a devotion to society's patient and a realization that society is made up of individuals that we are all concerned about as well.

That is why I mentioned, you know, what is the philosophy of public health because how do you really take those separate concepts of who the patient is and bring them together into some kind of coherent philosophy for us to practice public health by.

But with regard to intent, I mean I think your suggestion of forcing a statement of intent up front would help us even further. It would not necessarily solve the problem because I think reviewers have to be highly skeptical of those kinds of statements.

PROF. CAPRON: Sure.

DR. SNIDER: But I think if you are highly skeptical of those statements and grill the people who make those statements when things look a little bit funny, it is functional. It is functional. It is hard work but it is functional.

DR. SHAPIRO: Thank you very much. We do not have time this morning, unfortunately, for any more questions but I want to thank you once again.

I do want to make a comment, which I will

follow up with commissioners and perhaps with Dr. Snider also, and that is as I listened to this discussion and think about the problems that swirl around here, you made one analogy which I actually found very helpful and helped focus my mind on the idea that Alex also spoke about a moment ago and that is you talked about public health practice vis a vis medical practice.

What that led me to think about was that it is not necessarily true as we think this through, that research -- nonresearch is exactly the right dimension to use here or we do not really have to, if we want to think about it, be stuck with that.

It may be the best one in the end but the issue that Mr. Capron raised, which was the conflict of interest issue that surrounded it.

That was convenient to separate medical practice from biomedical research and so the two things kind of coincided with each other and it kind of flows out more or less nicely in that model but here we have the public health issue and there are

other issues like it which will come on next time where that kind of easy division that flows down the stream does not work and it throws me back at least to see how one could focus on the issue by thinking about where does that conflict arise and not whether it is research or not. Maybe it is exactly the wrong question.

Now we do not -- I do not know that I have thought this out carefully and I do not want to defend it now. We do not have time in any case but it is an issue which we will pursue in the next -- as we go along.

So really let me thank you very much. I found your remarks extremely interesting and helpful and I am very grateful for you being here this morning.

Let's go on then to our next panel with Paul Goebel and Duane Alexander if they both are here. Yes, they are.

Let me thank you both very much for being here this morning and being part of our discussion.

We very much appreciate the time you have taken.

If you do not mind, what we would like to do is go to your remarks first and we would like to hear from both of you and then go to questions. The commission is so full of questions I am afraid if we do it in reverse order we will not give your speaking equal time and opportunity. So we will just go in alphabetical order.

Dr. Alexander, welcome again and it is very nice to see you here this morning. Thank you very much for coming.

PANEL II: ESTABLISHMENT AND IMPLEMENTATION OF FEDERAL REGULATIONS

DUANE ALEXANDER, M.D., Ph.D., NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

DR. ALEXANDER: Thank you, Dr. Shapiro. Thanks for the invitation to --

DR. SHAPIRO: You have to press the button.

DR. ALEXANDER: Sorry about that.

Thank you, Dr. Shapiro. Thanks again for the opportunity to come once again before the commission.

For new investigators entering clinical research today, it sort of seems like the research regulations with human subjects have always existed, but obviously they did not.

As clinical research in the United States began its marked expansion in the 1950's and the early 1960's, they really had only to go on the Nuremberg Code of 1949 and the World Medical Association Declaration of Helsinki of 1964. That is basically all there was for general guidance.

Physician researchers paid at least lip service but there were no formal NIH or government requirements and institutions varied widely in their policies in the 1950's and early 1960's for protection of human subjects in research.

The first formal review procedures in the federal government for protection of research subjects were established in 1953 when a document called "Group Consideration of Clinical Research Procedures Deviating from Accepted Medical Practice or Involving Unusual Hazard" was issued in connection with the

opening of the clinical center at the National Institutes of Health.

This document showed particular concern with issues of how much risk to subjects was justified and what aspects of a study had to be disclosed to subjects. More importantly, it introduced the idea that resolution of such issues for any particular project had to be subjected to group consideration, although primary responsibility was seen as remaining with the investigator.

These original guidelines underwent several revisions but pertained only to the intramural program of the NIH, that is for the government employees on the NIH campus.

The use of institutional review boards as a regulatory mechanism for research supported by the department, derives from Public Health Service review requirements initiated in 1966 by the Surgeon General of the Public Health Service. There were two surveys in the 1950's that showed that some institutions had some type of review procedures prior to the Surgeon

General's requirements, but these procedures were certainly not uniform and not universal and were the exception rather than the rule.

In his memorandum establishing the institutional review requirement, the Surgeon General issued the following statement of general policy, and this is a quote from that memorandum: "Public Health Service supported clinical research and investigation involving human beings should be provided only if the judgment of the investigator is subject to prior review by his institutional associates to assure an independent determination of the protection of the rights and welfare of the individual or individuals involved, of the appropriateness of the methods used to secure informed consent and of the risks and potential medical benefits of the investigation."

This statement, it can be noted, explicitly assumed that the requirement pertained to biomedical research although a clarification issued by the Surgeon General later in that same year extended applicability to behavioral research.

The initial requirement was limited to Public Health Service supported research and was seen as supplementing the NIH peer review system that had evolved since 1947 for evaluating the scientific quality of research proposals.

A number of administrative changes in these Public Health Service review requirements were made in the years following the Surgeon General's memorandum.

The most significant change was a shift from the initial procedure under which a description of the review was submitted with each proposal to a system of general assurance of institution compliance with the requirements under which an institution sought one approval for procedures that would be applied to the review of any proposal within the IRB's jurisdiction.

In 1971, the well-known "Institutional Guide to DHEW Policy on Protection of Human Subjects" was published, establishing these Public Health Service requirements as department policy. Applicability was confined to studies in which subjects may be at risk, and though no longer limited to the Public Health

Service, remained confined to research supported by the Department of Health, Education and Welfare.

Broadened reach, however, was potentially applied because the Guide stated that if the Secretary judges that an institution has failed to discharge its responsibilities for the protection of individuals in its care, whether or not DHEW funds were involved, the Secretary may question whether the institution and the individuals concerned should remain eligible to receive funds from the department for activities involving human subjects.

Administration of the policy remained in the Institutional Relations Section of the Division of Research Grants of the NIH. Throughout, the Institutional Guide provided more detail and direction than had earlier Public Health Service statements.

This then was the situation in the early 1970's with regard to research with human subjects. A number of events occurred in those early years of the decade that made this a national issue.

First, in 1969 was the Strunk v. Strunk court

decision. This was a case involving the transplantation of a kidney from a minor to another member of the family with consent by the parents. The court decision ruled that the parents consent alone was not sufficient for a minor child to donate this kidney and court review was required. This sent questions throughout the pediatric research community about whether or not we might continue to do nontherapeutic -- nonbeneficial research on children without court review.

This fear was heightened with Paul Ramsey's publication of his book in 1970, The Patient as Person, in which he argued forcefully that any nontherapeutic research on children was absolutely unethical, a further challenge to pediatric research in a nonbeneficial context.

There was a Neilson case in 1973 in which a lawyer on the IRB from the University of California, San Francisco, made similar claims that there was no authority of parents to give permission for their children to undergo any nonbeneficial research.

In 1973 there was national attention focused in Congress on the sterilization of the Ralph sisters. Two minority girls who were mildly retarded who were sterilized with apparently minimal consent and knowledge of their parents and certainly no involvement of them. Even though this was not research and it was clearly just practice, it was highlighted in a research context and raised issues about research on the mentally infirmed.

The big case was the Tuskegee syphilis study and disclosures about that in 1973. There was also discussion and concern regarding drug testing on prisoners, psychosurgery as medical practice, and research on minority groups in general.

But the crowning blow that forced congressional and national action on this was the Roe v. Wade Supreme Court decision of 1973 and bringing in the issue of fetal research. Hostility of some members of Congress to this decision on abortion found an outlet and a scapegoat in research on the fetus with Congressman Angelo Roncallo, Senator William F.

Buckley and others rallying on the floor of the Congress against reports of some of the studies conducted and introducing legislation to ban all or parts of such fetal research. This was the final straw that brought action.

Under the leadership of Senator Edward Kennedy, who really has never been given adequate credit for the key role that he played, all these concerns were packaged together and handed to a national commission to resolve. This action got it out of the political arena, off the floor of Congress, which is often the worst place for a rational debate to occur, and off of the national agenda for four years while the debate could cool off.

The commission provided a vehicle for other -- for sober reflection, consideration of the issue based on data and facts, and an opportunity to seek consensus in a public process.

Creation of the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research by Public Law 93-348 signed on

July 12, 1974, was a brilliant, if not novel, strategy and really helped preserve the medical research enterprise in this country.

The Executive Branch had not been idle during all this time of debate and turmoil. Spurred initially by the need for guidelines in response to applications to the NIH for research on the fetus and later expanding to cover research involving subjects with restricted ability to give consent. An active process of research regulation development was underway at the NIH.

This process was initially intended as guideline development and then as regulation development and then as it was caught up in events came to be the production of a draft document for public comment to serve as a basis for discussion by the National Commission.

This process was led at the NIH by Dr. Charles Lowe, who was scientific director of the NICHD; Dr. Ron Lamont Havers, deputy director of the NIH; and Dr. Chalkley, who was chief of the

Institutional Relations Branch in the Division of Research Grants, the predecessor of today's Office for Protection from Research Risks.

They assembled an outside advisory group of researchers, ethicists and lawyers, who discussed the issues and provided recommendations that were turned into draft regulations. The proposed regulations for research overall and with adults based largely on the institutional guide were published in October of 1973. The draft regulations for research involving children, the abortus, in vitro fertilization, prisoners and the mentally infirmed were published for comment in November of 1973.

Soon thereafter it became clear that there would be a national commission so no further action was taken on the latter guidelines until the commission made its recommendations. In anticipation of the legislation, final regulations for protection of human subjects in general were issued by DHEW on May 30th of 1974 as 45 CFR 46 and, as subsequently amended several times, have governed DHEW and DHHS

policy for research. Public Law 93-348 required such regulations but they were already issued as final regs before this legislation was passed.

It was on this tide that the National Commission found itself afloat when it first met in December of 1974. Bob Levine, who you have heard testify a number of times, Bonnie Leigh, who is here, and I were fortunate to be members of the staff of that commission. I had major responsibility for assisting with the reports on research on the fetus and research involving children.

The commission got off to a good start by electing as its chair Dr. Ken Ryan, Chair of the Department of Obstetrics and Gynecology at Harvard, and under his wise guidance and steady hand, the commission agreed to make every effort to achieve consensus, correctly perceiving that a series of widely split votes and minority reports would accomplish little.

Their personal interactions and attempts to understand individual concerns and work to resolve or

accommodate them as they reasoned together were in many ways responsible for the general acceptance of the commission's recommendations by the research community, advocacy groups and the government.

The commission had to grapple with research on the fetus as its mandated first charge to be accomplished in four months. They managed to do it in five. The recommendations were quickly turned into regulations and the congressionally imposed moratorium that existed on fetal research was lifted.

The other topics took longer.

Probably the most important provision of Public Law 93-348 was the requirement that the commission make its recommendations on each of its charges to the Secretary of the Department of Health, Education and Welfare, who then was mandated to publish them and respond by either issuing regulations to implement the recommendations or justify why that action was not being taken so there was no way that the reports of this commission could sit on the shelf and gather dust.

To its credit, the department influenced largely by Assistant Secretary for Health Ted Cooper made the decision at the outset to develop and issue proposed regulations that would essentially implement the recommendations of the commission and publish them together with the commission's report for public comment as a notice of proposed rule making. This meant rapid drafting of proposed regulations.

A team that was headed by Dick Riesberg and Joel Mangel from the Department's General Counsel Office and Public Health's General Counsel's Office, with membership largely from NIH and then ADAMHA, Alcohol, Drug Abuse and Mental Health Administration, did the drafting.

I served as the unofficial go between from the commission staff to the drafting group. With few exceptions, the proposed regulations for research implemented exactly the recommendations from the commission. Some changes were made based on public comments when the final regulations were issued but the commission's regulations are easily recognizable

today.

The full process was a long one although it was published within the required 90 days. For example, the proposed children's research regulations were published in 1977 but not finalized until 1983.

The commission issued separate reports on each of its charges so subparts were added to the general regulations at 45 CFR 46 for each special group in turn.

First, as mentioned, was the fetus. Here the department issued subpart B covering not just the fetus but pregnant women and in vitro fertilization as well. New concepts here were the idea of the equivalence of the fetus going to term and the fetus scheduled for abortion with the idea that you could, due to the fetus scheduled for abortion, do only things that would be acceptable for a fetus going to term except that, if you made the decision that it was acceptable for a fetus going to term, you could preferentially select for the study fetuses scheduled for abortion because if there were risks it would have

less consequences.

It also introduced the concept of an ethics advisory board to provide interpretation and exceptions to the regulations if needed.

The response to the report on research involving prisoners led to subpart C. This was the major deviation from the commission's recommendations. Originally, most of the commissioners had total opposition to the idea of drug testing being allowed on prisoners. There was a hearing in which we had testimony from a prisoner who had participated in drug research, a prison warden, and people doing research in prisons.

We also arranged a site visit for the entire commission to the Jackson State Prison in Michigan, which was the site of a major amount of drug testing being done in prisons in the United States.

As a consequence of this, commission members softened their stance and their recommendations provided permission for such research and very strict controls and regulations were drafted to implement

that.

However, Secretary Califano was personally very opposed to prison research and he directed revision of these proposed regulations so that they essentially banned research in prisons except for research on incarceration or research that would be beneficial to the prisoner themselves. The net effect of this has been the removal of virtually all research from prisons, including much of the research on incarceration itself.

Response to the report on children was subpart D. The new concept here arising from the commission was really the concepts of assent and permission as opposed to informed consent. With "assent" to be derived from children, particularly if they -- especially over age seven, and permission, not consent, to be given by the parents.

The response to the report on the institutionalized mentally infirmed was proposed -- developed into regulations for comment. There was extensive protest and objection from much of the

research committee to these as well as from the advocacy community. No consensus was reached and no regulations were ever finalized for research in persons who are mentally infirmed.

The response to the IRB report was really an indication that much of what the commission reported had already been implemented with the regulations and minimal changes were made.

The commission ended its work in 1978. Developments since the Institutional Relations Branch was changed to the Office for Protection from Research Risks, an independent and highly elevated agency, most recently that has been changed further to separate it from the National Institutes of Health and put it under the Assistant Secretary for Health.

There has also been development of the Common Rule, expanding the regulations applicability from the Department of Health and Human Services to most federal agencies. This was a process that took many years and was extremely difficult. Most federal agencies are now in but not all.

There were technical revisions made to the regulations in 1991. Congress repealed the requirement for an ethics advisory board to review in vitro fertilization research in 1993 because the department had refused since 1980 to establish the ethics advisory board that its own regulations required and had provided an obstacle to any department's support of in vitro fertilization research.

Most recently a proposed revision to subpart B has been published by the department for public comment and work on that continues.

One measure of the success of this process is that in the ensuing 20 years we have moved from erecting barriers to inclusion of children and certain other classes of subjects in research because the research was perceived as a threat or a hazard to a situation in which we demand that those barriers be torn down because they exclude those populations from the benefits of research. This happened first with women and minorities and now has happened with

children.

The big change in this situation came in the early 1990's from two events that were made possible, in part, by the success of the research regulations that the department implemented based on the commission's recommendations.

First, augmented by AIDS activists, the pendulum had swung from research being viewed as a burden to be avoided to a benefit to be sought and not denied.

Second, the women's health movement built on this feeling and made exclusion of women from some highly visible clinical studies a cause c¾lÀbre.

As a consequence, the Congress actually mandated the NIH to include women and minorities in all clinical research done with NIH support. Guidelines to do so were developed and implemented in 1995 with rigid review and reporting requirements.

Last year, in response to requests from the American Academy of Pediatrics and the pediatric research community, not from directives from Congress,

the NIH did the same for children.

That is the basic story of how the current regulations were developed and evolved. I will be glad to try and answer your questions during the discussion period.

DR. SHAPIRO: Thank you very much for getting so much in, in a rather really brief time. I very much appreciate it.

I have asked commissioners, however, to hold their questions until we have heard from our second panelist here today and then we can have questions for both.

Mr. Goebel?

PAUL W. GOEBEL, Jr.,

FOOD AND DRUG ADMINISTRATION

MR. GOEBEL: Thank you very much, Dr. Shapiro.

(Slide.)

The first protection for -- next slide, please.

(Slide.)

I do have overheads.

The first protection for consumers of foods and drugs began when President Theodore Roosevelt signed the Pure Food and Drug Act in 1906. The 1996 Act had no requirement for FDA preclearance of any kind before a new food or drug product could be introduced into the marketplace. FDA's primary emphasis was to analyze marketed products for adulteration and safety.

(Slide.)

And the next.

(Slide.)

I am sorry. I am not keeping up with these slides.

The 1937 -- in 1937 a new wonder drug, Elixir Sulfanilamide was starting to be used but something was wrong. Children were becoming sick and dying and the new drug was a suspected cause. The University of Chicago was charged with performing toxicity testing of the sulfa product. A graduate student named Frances Kelsey was in charge of watching the rats. It

soon became apparent that the rats were in trouble. Even the most rudimentary premarket testing would have quickly detected the poison which was ethylene glycol, now commonly used as antifreeze.

The deaths of over 100 children was the final push Congress needed to pass the 1938 Food, Drug and Cosmetic Act after over five years of wrangling. The law contained the first requirement for toxicity testing before a new drug could be marketed.

(Slide.)

In 1962 a FDA medical reviewer needed more assurance before allowing thalidomide to be marketed. That reviewer was Dr. Frances Kelsey. The subsequent discovery that thalidomide was the cause of deformed infants helped convince Congress to pass the 1962 Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act.

These amendments required clinical research to show efficacy as well as safety, a thirty day requirement for FDA review of the study before it was started, and controlled distribution of

investigational drugs.

That Dr. Kelsey was present at both of these events and that she is still working at FDA today illustrates how recently these safeguards were put in place.

The 1962 law also contained the first federal requirements for informed consent. However, informed -- at that time informed consent was not considered to be a major part of the Act. The requirement was inserted at the last minute as a result of an incidental comment by Senator Javits. It allowed an exception from informed consent when the clinical investigator determined that consent was not feasible or contrary to the subject's best interest.

A 1967 FDA policy statement outlined for the first time how consent should be obtained and what it should consist of. Also, for the first time it specified that consent should be obtained in writing for Phase I and Phase II studies but continue to allow oral consent with a notation in the clinical record for Phase III studies.

The first FDA regulations requiring IRB review became effective in 1971. IRB review was required only for subjects who were in a hospital or other institution.

(Slide.)

FDA inspections of IRBs and clinical investigators showed that study subjects were not being adequately protected. The existing regulations did not contain sufficient guidance and authority for adequate correction of the problem.

In 1981, FDA and HHS issued similar regulations which outlined the organizational and procedural requirements for IRBs and informed consent.

These regulations codified many of the recommendations of the first national commission.

Separate regulations were issued because of the differences in authority between HHS and FDA. The 1981 FDA regulations extended the requirements for IRB review and informed consent to all FDA regulated clinical studies. These regulations continue largely unchanged. There have been some amendments and are

identical in most respects to the Common Rule.

(Slide.)

An exception was included in the 1981 regulations for use of a test article without consent in an attempt to save the life of an individual but this provision does not appear to provide for planned research or for randomized study in an emergent situation.

FDA believed it was important to determine the safety and efficacy of drugs, biologics and medical devices used in emergent circumstances through well designed and well conducted studies.

(Slide.)

Therefore, FDA issued regulations in 1996 providing for the waiver of informed consent for planned research intended to be conducted in emergency settings.

(Slide.)

This waiver is invoked when it is not possible to obtain informed consent from the patient and there is no time to locate a legally authorized

representative before the research intervention must begin.

Additional safeguards such as community consultation and public disclosure are required as an alternative to individual informed consent.

(Slide.)

FDA regulated research: FDA regulates a large amount of human subjects research that is conducted to determine the safety and effectiveness of new products regulated by FDA. Primarily drugs, biologics and medical devices. This research is usually not performed or funded by FDA but by those who have a proprietary interest in marketing the products.

It is performed under a research permit either in an investigational new drug application, IND, for drugs and biologics or an investigational device exception, IDE, for medical devices.

FDA has jurisdiction over these studies because the test article is regulated by FDA. FDA does not have authority to withhold funding for this

research but may refuse to consider the study data in support of a marketing permit. FDA may suspend an IRB or disqualify it from reviewing studies of FDA regulated products.

(Slide.)

The Common Rule is -- per se is not enforced by FDA but the FDA regulations closely parallel the Common Rule. The FDA Human Subjects Regulations are 21 CFR Part 50, informed consent, and 21 CFR Part 56, IRB constitution and function.

The FDA regulations do not include detailed requirements -- the detailed requirements for fetuses, in vitro fertilization, pregnant women and prisoners that are outlined in subparts B, C and D of the HHS regulations, 45 CFR 46.

FDA has no registration requirements or assurance process but FDA is notified of the names of the IRB through the research permit application. FDA performs on site inspections of IRB's that review and approve this research.

The inspections are -- a priority for

inspection assignments are first IRB's that were out of compliance in the previous inspection, follow-up -- second, follow-up to complaints received by FDA. Three, IRB's not previously inspected. And, four, routine reinspection of those IRB's in our inventory.

FDA plans to reinspect IRB's at intervals from one to five years after the previous inspection.

In addition, when studies are submitted to FDA for a marketing permit the IRB's of record for that study may be assigned for inspection. This is usually done if we do not have a current inspection result for that IRB or there may be a special issue that is study specific.

Inspections are assigned by one of three centers within FDA, drugs, biologics and devices, and are performed by the FDA field investigators in 21 district offices throughout the country. Inspection reports are reviewed by the assigning center.

(Slide.)

Clinical research performed outside the U.S. if it is drugs and biologics research done under an

IND it should be in compliance with the FDA Human Subject Protections Regulations. If it is not done under and IND, scientifically valid study data may be accepted after the fact by FDA. Both drugs and device regulations require such foreign research to be done in compliance with the Declaration of Helsinki or the laws of the country in which the study is performed, whichever provides greater protection for the human subjects of research.

FDA does inspect pivotal studies performed by foreign clinical investigations when there are no comparable studies performed in the United States.

(Slide.)

FDA does not perform on site inspections of foreign IRB's or their equivalent committees.

For guidance FDA centers that review research conducted in clinical studies, primarily the drugs, biologics and devices again, have numerous guidance documents that have been published and are posted on the FDA web site.

Much of this guidance pertains to the

scientific aspects of how the studies are to be done and does not address the human subject protection issues but I have listed several documents that pertain to the protection of human subjects.

Our primary guidance document is the FDA information sheets, guidance for institutional review boards and clinical investigators. These are interpretation of how the regulations can be met for -- and has been quite useful for clinical investigators, IRB administrators and IRB members.

The second document is the International Conference on Harmonization Good Clinical Practice Guidelines. This was published in 1996. The International Conference is made up primarily of the U.S., European Union and Japan, and consists of the regulators of those countries and the drug manufacturers -- representatives of the drug manufacturers of those countries.

The guideline was published by FDA as guidance, which means it is not enforceable but we think it would be a good idea to follow the guidance.

This ICH guideline is becoming a -- seems to be becoming a worldwide standard for conducting drug trials and this process is being driven by the sponsors who write in their contracts that compliance with ICH is one of the conditions for conducting the study.

We also have a guideline for the monitoring of clinical investigations. This is a very short guideline that outlines the responsibilities of sponsors in monitoring the studies that they are having done.

Computerized systems used in clinical trials. This outlines the validation required for paperless systems used in clinical trials and it is also applicable to IRBs if they go to paperless systems.

There is -- devices has a guideline -- guidance on investigational device exemption, policies and procedures. They also have background information for international officials on the regulation of medical devices.

We do have differences between the FDA and

HHS regulations that are included in the information sheets. Of note are the differences in the definitions of research. The FDA regulations do not define research. We define the clinical investigation. And in the case of drugs, as an example, any use of a drug, except for the use of a marketed drug, in the course of medical practice is clinical investigation.

(Slide.)

We have in the information sheets also a self-evaluation checklist for IRBs which has references to all of our regulations that apply.

(Slide.)

FDA also conducts research. Its employees conduct research or FDA funds a small amount of research. This is included in the purview of the HHS regulations and FDA has negotiated a multiple project assurance with OPRR to cover this research.

All research funded by FDA or conducted by FDA employees is required to be in compliance with 45 CFR 46. There is research that is funded by FDA but

not conducted by FDA employees and these are the orphan products. These are rare diseases whose anticipated sales would not cover the cost of conducting the research that is required.

(Slide.)

FDA funds this research. It is not reviewed by FDA's IRB, but the FDA's contracts office receives assurance of compliance with 45 CFR 46 before the funds are released to the study site.

(Slide.)

We have other research that is sponsored, funded or supported by FDA or conducted by FDA employees, and this research is reviewed by our IRB. The IRB operates according to the multiple project assurance and reviews all of the research. It is the IRB on record unless there is an IRB with an OPRR assurance at the study site.

(Slide.)

To give you an idea of how much research is conducted, last year our IRB reviewed 12 studies, so it is not a lot.

We do have -- I think this slide illustrates -- that when an institution with a multiple project assurance performs research with an FDA regulated test article, they have to comply with both the FDA and HHS regulations. This is do-able but it is a unique situation.

Thank you very much.

DR. SHAPIRO: Thank you. And thank you very much for the very comprehensive outline you have given us with the history in this matter with respect to the FDA. We very much appreciate the effort. And thank you very much for distributing the material that we have now distributed to each member of the commission. That is very helpful to have.

Let me now open up for questions for either of our guests from members of the commission.

Alex?

DISCUSSION WITH COMMISSIONERS

PROF. CAPRON: Dr. Goebel, I would like to know: the document that you described, the differences between the FDA and HHS regulations, has that been

supplied to the commission?

MR. GOEBEL: Yes, it has. I have supplied all of the documents. I supplied one copy of all the documents and I understand those will be produced for you.

PROF. CAPRON: All right. I think it would be interesting after we have reviewed that to hear further from you or from other people at the FDA about what barriers exist, if any, to more fully integrating the two systems. It does seem as though the major objective that the President's Commission had in recommending what became the Common Rule was to avoid the difficulties for investigators and IRBs of having potentially different systems in place and the confusions that can follow from that, so I hope we can return to that.

I have two other questions that are raised here. You say that because you do not have the equivalent of Parts B, C and D that in research that you do not sponsor but that is commercially sponsored there are not any regulations that particularly speak

to that from the FDA side. What happens? Suppose someone is developing a product that involves something that would fall under those regulations but it is privately sponsored.

MR. GOEBEL: FDA does not have the authority to enforce Subparts B, C and D but we do point to them as guidance if people say, "How should we do this?" We say, "Well, here is guidance."

Our regulations also say that, as does Subpart A of 45 CFR 46, that there should be additional protections included for vulnerable categories of subjects. It is just that FDA does not specify what those protections -- our regulations do not specify what those protections should be.

PROF. CAPRON: Well, I hope as part of the process I just described a moment ago we get some explanation for why over the 20 years that those parts have basically existed in one form or another. The FDA has not adopted equivalent regulations and gone beyond the generalized language about vulnerable populations.

The other question I had was about your inspections and it is two questions connected. You say these are done under the regional offices and I wondered how they are standardized or how the reports are integrated.

MR. GOEBEL: We do have a -- thank you for that question. We do have a -- what we call a compliance program and that outlines in detail what should be verified by our inspectors when they are on site and this is standardized. It is updated periodically. Also, the field investigators that do these inspections by and large are specialists in this area and they also specialize in -- most of them also do inspections of data audits of clinical investigators. We do have training programs periodically to make sure they are current in their knowledge.

PROF. CAPRON: Your answer in a way gets to the second part of the question. Some 20 years ago when we were looking at this with the President's Commission and the FDA system was more in its infancy

as to the role of IRBs, the people conducting those on site audits were people who also had just general responsibilities as field investigators. They could be going to a tuna fish factory one day and whatever. I gather that that is not the case now or is it partially the case in some regions or how is that?

MR. GOEBEL: Well, as I said, the -- we have people that specialize in this area and those are the people that are called on first to do that. It could happen that for some reason a fully trained person is not available and someone else may be sent. More commonly we would send a person as a trainee along with an experienced individual for the first two or three times and they could get training that way.

PROF. CAPRON: And what percentage of the FDA inspectors are specially trained to do IRB inspections? Do you know?

MR. GOEBEL: I can refer that question. I do not have that at my fingertips.

PROF. CAPRON: Thank you.

DR. SHAPIRO: Thank you.

Diane?

DR. SCOTT-JONES: I have three questions. The first two are for Dr. Alexander.

This question is similar to Alex's. He asked about Subparts B, C and D of 45 CFR 46. Is it the case that no other agency outside your own signed on to those subparts? So no other agency signed on to those, is that right?

DR. ALEXANDER: They are certainly DHHS-wide and I think they are part of the Common Rule but I will have to ask -- maybe Gary Ellis can tell us what the Common Rule is.

DR. SCOTT-JONES: They are not.

PROF. CAPRON: Part A.

DR. ALEXANDER: Part A is.

DR. SCOTT-JONES: Education did.

DR. MESLIN: Gary can give you the answer to that.

DR. ALEXANDER: I do not have that.

DR. SCOTT-JONES: Okay.

DR. SHAPIRO: Gary, welcome again.

DR. ELLIS: Thank you. I believe that Subpart A is common today to 17 federal departments and agencies as a matter of either regulation, statute or executive order, and subpart D is common to the Department of Health and Human Services and the Department of Education by regulation.

DR. SCOTT-JONES: Okay.

Then my next question has to do with the special regulations for children. I am interested in your view on whether those regulations for children are appropriate for adolescents also.

DR. ALEXANDER: I believe that they are. There are -- certainly in the report from the commission there was advice that the IRB and investigators should take account of the growing maturity of children and adolescents and provide greater reliability on their views as to whether or not they might participate in research, and greater opportunity for them to give -- greater reliability on their assent and less perhaps than the permission of their parents.

There is also provisions in there that allow for participation of so-called emancipated minors without the parent's permission in certain specified instances. So I believe that overall we can provide, under the current children's regs, appropriate respect for adolescents as they participate in research.

DR. SCOTT-JONES: And my last question is for Dr. Goebel. Because you do not follow the special regulations for children, could you say a little bit about approximately what percentage of the research that you regulate would involve children and what is your view of whether children are adequately considered when the research is conducted?

MR. GOEBEL: Up until -- I believe it was 1998, very little -- very little research involved children but there was a change in the FDA regulation that now requires labeling for children to be included in all newly approved drug products.

Whenever the study data that is done in adults can be extrapolated to children, that is what we encourage. However, there will be an increase in

research done in children to show safety and efficacy of certain products. We are considering adding Subpart D to our regulations to cover this contingency where -- because we realize that there -- that it would be helpful to both the industry that is conducting the regulations and as added protection to have specific requirements present.

But at this time it is not done and I do not have a percentage of studies. I am not sure how easy that would be to obtain. Hopefully, that will still be rather small because, as I said, if we can get the data by extrapolation, that is the preferred method.

PROF. CHARO: May I put on your list, Harold?

DR. SHAPIRO: You are talking, Alta. Let's go.

PROF. CHARO: Oh, okay.

First for Dr. Goebel. One of the things that we have seen a lot in our IRB at Wisconsin is research that involves off-label usages of marketed drugs and there are other settings in which this does not wind up going through the IRB because there is little

incentive for the companies to do so unless they are looking for a relabeling.

In light of the recent changes in the rules concerning publicity surrounding off label uses in the form of things like academic papers that are being presented, has FDA had any occasion to consider the oversight of research involving off-label use that does not go to an IRB because it does not involve an investigator in an academic center? Whether it is going through a private IRB or through no IRB at all?

MR. GOEBEL: Well, our position is and has been for many years that a physician may use a drug product for a use that is not described in the label and under his or her authority to practice medicine for treatment and when the intent is not research.

When the intent is research then it should have IRB review and informed consent. We do have a regulation that has five conditions that can be looked at for determining whether a marketed drug needs to come to the agency in the form of an IND submission or whether the research can be done without submitting

anything to FDA.

PROF. CHARO: Okay. Thank you.

The second question was actually for Dr. Alexander. You made allusion to the changing paradigm of research moving from one of concern about exploitation to one of concern about lack of access and I wondered if you were trying to suggest that the thrust of the regulations ought to be changed overall?

I ask this because although that certainly has been a perception out there, I do not know of anything empirically that would suggest that the vast majority of research now really does offer the prospect of a distinct benefit to the participants.

I am somewhat concerned about a wholesale move towards a new paradigm.

DR. ALEXANDER: Clearly there are different types of research that have different degrees of benefit to participants. I think the thrust of the regulations which are designed to protect human subjects really must stay the same. The thrust is

protection and the language is couched in such terms.

But at the same time there needs to be, I think, recognition of the permissiveness of participation on the part of any individual and the overall focus, I believe, should be on allowing maximum opportunity for individual decision making for participation in research.

I think, for the most part, the rules do that. There are a few places perhaps here and there where that is not quite the case, but my personal belief is that overall we should provide a structure and a framework that provides the maximum information and capability and increasing capacity for individual decision making in research, and protection of individuals who are vulnerable and do not have that full capacity for decision making.

But overall, I think that what is existing at present probably does not need to be changed in a general approach of protection, as well as allowing people to participate once they have adequate information.

PROF. CHARO: Thank you.

DR. SHAPIRO: Thank you.

Other members from the commission at this time?

Eric?

Marjorie?

DR. MESLIN: My question is for Dr. Alexander. In your remarks you had referred to the forcing clause that the National Commission had at their disposal and you described some of the effect of having that authority. I wonder if you could share with us some of the positive and negative effects of having that authority and making recommendations and seeing them through?

DR. ALEXANDER: Well, this is a clause that I think any commission would love to have. It is a guarantee against ignoring the reports that a commission puts forward. It is unusual to have this in legislation that a commission gets and I think that in these particular circumstances it worked to everyone's advantage to have it.

It is all too easy to let recommendations from any commission lie on a shelf unresponded to. Here there was not just a requirement for a response of some type, but to develop regulations to implement unless there was justification given not to. That is really powerful and so I think that that additional prodding from that legislation certainly gave the department pressure to respond and do something that I think it wanted to do anyway.

I mean, there was -- as I said, the basic regs were in place from the department before the legislation passed, but would we have gotten the subparts B, C and D without the requirement for response from the department in terms of issuing regulations, implementing the recommendations or saying why not?

I think probably that is an open question. Probably -- clearly we would have on the fetus because there was pressure to go ahead there with doing something. Probably we would have with children because there was enormous pressure to do something

there. Whether we would have for other groups I do not know. Even with that pressure we wound up never getting final regulations for research with subjects who are mentally infirmed.

DR. SHAPIRO: Thank you.

Other questions? Yes?

PROF. CAPRON: For the historical record, of course, you did not get the children's recommendation until the President's Commission came along with its action forcing power and said, "Why haven't you adopted the children's regulations, or some modified equivalent, if you had objections which you faced on those?" It was not until we got, without action forcing power, to the subjects of research with the mentally disabled that the subject again began to percolate, and now NIMH has taken a number of steps, which again maybe it was going to take and maybe it was not without us.

The only other thing I would note is that to the extent that you do anything further with those remarks, would it be historically the case that what

you describe as the group that was assembled by the department in '73 and '74 to develop those regulations was not a group in the sense of a committee? We were all independent advisors and, therefore, we did not meet in public.

DR. ALEXANDER: That is correct.

PROF. CAPRON: Unlike other advisory bodies.

DR. ALEXANDER: Alex knows that well because he was one of the ones involved with that process.

DR. SHAPIRO: Marjorie, you have a question?

DR. SPEERS: I am going to pass.

DR. SHAPIRO: Any further questions, members?

Diane, yes, of course. I am sorry. I had you on the list. I apologize.

DR. SCOTT-JONES: This question is for Dr. Alexander or Dr. Ellis. Why weren't the children's regulations approved until 1983? Was there a reason or just inertia or what was it?

DR. ALEXANDER: I guess you were involved in those.

I do not think there was any one particular reason. It was just the slow grinding of a process that takes a long time in reaching consensus and agreement not just from one agency but different agencies of the department. We had the CDC. We had ADAMHA. We had the FDA participating as observers although not directly from the regulatory standpoint, so it took a while and there was a lot of public response to that -- this particular publication of recommendations and a fair amount of controversy in that public response that all had to be dealt with.

The process was perking through. The statement that we got from the President's Commission gave it a kick in the pants that moved it a little faster. It probably would have gotten there eventually but it probably would not have been 1983 without that prodding.

DR. SHAPIRO: Thank you.

Any further questions from the commission?

If not, let me thank you both very much. It has been really very helpful to have this perspective.

I appreciate you taking the time to be here today.

I am going to propose that we just keep moving straight on through our agenda here this morning, that is assuming that our next guests are actually here since we are a few minutes ahead of time and that is Dr. Forcino, Rodriguez and Dr. Burris.

Are they here? If so, if they could just come forward and just pick any one of these seats in front, that would be helpful.

PANEL III: PERSPECTIVES FROM OTHER AGENCIES

DR. SHAPIRO: Thank you very much. As you know, this next panel is concerned with perspectives of other agencies in the matters we have been discussing this morning, at least some of the other agencies. We have at least two of our panelists who are here now since we are running a little ahead of time. We will, I think, just get started and follow the same patterns we did just a few moments ago, that is listen to our guests, and then go to questions from there.

Let me start with Dr. Burris from the

Department of Veterans Affairs.

Dr. Burris?

JAMES BURRIS, M.D.,

DEPARTMENT OF VETERAN AFFAIRS

DR. BURRIS: Thank you. I am the deputy to the chief research and development officer of the Department of Veterans Affairs, Veterans Health Administration.

And, also, in the audience today is Joan Porter, I think known to most of you, who has recently been appointed as the executive officer for the Office of Research Compliance and Assurance, a separate division of the Veterans Health Administration, which is part of the Office of the Undersecretary for Health. I will be referring to that office in a few moments as I discuss the human subjects protections in the Department of Veteran Affairs.

The department implements the Common Rule for protection of human subjects of research under Title 38, Part 16 of the Code of Federal Regulations. This part is the VA counterpart of 45 CFR 46, Subpart A,

the Department of Health and Human Services basic policy for the protection of human subjects.

We do not at the present have a formal regulation that is the counterpart of B, C and D subparts of the DHHS regulation. We do, however, incorporate additional protections for several categories of vulnerable subjects under our research policy manual, M3-Part 1.

And in addition, in April of 1998, the VA established a regulation mandating treatment of research related injuries that are incurred by human subjects participating in VA research. This is 38 CFR, Part 17, Section 17.85, and that is also among your handouts today.

VA research and development is an intramural program. The funds that are appropriated for medical and prosthetic research are allocated to VA employees on the basis of a nationally competitive merit review process to conduct research in VA facilities on high priority health care needs of veterans.

VA investigators may also obtain support for

their research from other federal agencies, from foundations and voluntary agencies, and from commercial entities, but all research that is conducted in VA facilities or by VA investigators is subject to VA and other federal regulations and policies.

Each VA facility that conducts research involving human subjects is required to establish a human subjects subcommittee that serves as the institutional review board. The composition, responsibilities and operations of the human subjects subcommittee are prescribed in the research policy manual and are essentially identical to the Department of Health and Human Services Guidelines for IRBs.

The Human Subjects Subcommittee is a subcommittee of the Facilities Research and Development Committee, which also has responsibility for such things as the Animal Care Program and the Biosafety Program, and space allocations for research.

The R&D committee must review and approve the minutes of Human Studies Subcommittee meetings. The

R&D committee has the authority to disapprove or restrict a study that has been approved by the Human Studies Subcommittee, but may not overturn a decision by this subcommittee to restrict or disapprove a study.

The associate chief of staff for research and development at the facility is responsible for logistic support of both the Human Studies Subcommittee and the Research and Development Committee and for assuring that they operate in compliance with all federal regulations and policies.

As an alternative to establishing its own human studies subcommittee, a VA facility may arrange to use the services of an IRB established by a medical or dental school that is formally affiliated with that facility. And 105 of the 120 United States medical schools are affiliated with one or more VA hospitals. There are about 150 or so separately administered VA health care facilities formerly called hospitals or medical centers.

In the case in which a facility does elect to

use the IRB at an affiliated academic institution, the IRB must include at least one VA employee as a member and must agree to comply with the provisions of 38 CFR 16.

The Research and Development Office at VA Central Headquarters in Washington, D.C., which is where I am located, is responsible for establishing research policies and procedures for allocating appropriated funds and for overseeing operations of the VA Research and Development Program as a whole.

The recently established VA Office of Research Compliance and Assurance that I referred to a moment ago is responsible for establishing policies and procedures to assess compliance with human subjects protection requirements. It promotes continuous quality improvement in human subjects protections, investigates allegations of noncompliance, and recommends sanctions to the VA's Undersecretary for Health when appropriate.

VA accepts multiple project assurances that are established by VA facilities, either alone or

jointly with their academic affiliate, with the Department of Health and Human Services Office for Protection from Research Risks. We consider those to provide the human subjects -- the assurance of human subjects protections that is required for the Secretary under the provisions of the Common Rule.

VA does also issue VA multiple project assurance contracts to VA facilities that do not have an OPRR multiple project assurance and those are intended to cover VA funded research and also all nonfederally funded research at those facilities and they are obliged to submit single project assurances to OPRR for individual Department of Health and Human Services funded projects and similarly to submit single project assurances to other federal agencies.

VA is currently in the process of establishing a contract for an external accreditation process for human subject protection programs in all VA facilities that conduct research involving human subjects. It is anticipated that this accreditation will be analogous to the JCAHO accreditation for

clinical programs or the AAALAC accreditation for animal care programs.

That concludes my remarks.

DR. SHAPIRO: Thank you very much and once again thank you for being here. Let me turn to Dr. Forcino first from the Department of Defense and then we will come back to questions later. I hope in the interim Ms. Rodriguez will also be here.

Dr. Forcino?

DOUGLAS FORCINO, M.D.,

DEPARTMENT OF DEFENSE

DR. FORCINO: Thank you.

Dr. Shapiro, members of the commission and members of the audience, first of all, I would like to say thank you for the opportunity to present the programs of the Department of Defense in the area of protection of human subjects from research risk.

I am fairly new to this job, having been in it for about four or five months, so there is very much that I do not know. I am learning as I go but fortunately in the audience today are my predecessor,

Dr. Ed Lane, whom I think many of you know, and also Dr. Al Graziano from the Office of the Surgeon General of the Air Force, and with our permission if there are questions which I cannot answer I would like to call them to a microphone to provide those answers for you.

DR. SHAPIRO: Absolutely.

DR. FORCINO: Also I have brought some overheads and with your permission, sir, I would like to move forward and use the overhead projector.

DR. SHAPIRO: Absolutely. Can we help you with the overheads? We have someone here who can -- or do you want to come over here? It is okay. You will just have to sort of speak into this microphone here or one of these.

You have one. Okay. All set. Thank you.

(Slide.)

DR. FORCINO: Thank you again.

Good morning.

Are you able to hear me in the back?

Okay. Thank you very much.

Again, I am Doug Forcino and I work in the

Office of the Deputy Undersecretary of Defense for Science and Technology. I always hate to begin a presentation with a disclaimer but one of the things that I have to say to you is that --

(Slide.)

-- and partially because I am so new, occasionally I offer my own opinions and this is going to be primarily a factual briefing but you need to be aware that any opinions that are offered are strictly my own and not official opinions or views of the Department of Defense.

(Slide.)

I was asked to basically comment on three sections of the Department's program for protection of human subjects, a little bit about the history and I will present that as much as I know of it, regulations and directives, and then how we implement our policies.

(Slide.)

This is a thumbnail sketch of the history basically. There are four things provided here.

Certainly there is a lot more, but I can provide those details for you as I learn them or as I find them at a later date.

It is interesting to note that as early as 1953 the Department of Defense had regulations that in general required volunteers to be informed of the risks of any type of research in which they participated.

Another landmark in 1975 is when the Department of Defense stopped chemical and biological weapons-related research on human subjects.

In 1983 we published a directive, Department of Defense Directive 3216.2, which is based upon -- and you will see why I say based upon in a few minutes -- the provisions of the Common Rule that had already been adopted by Health and Human Services and by the FDA.

We had not yet in the Department of Defense adopted the Common Rule. In fact, we did not do it until 1991 so we did not have a Department of Defense Common Rule on which to base our directive, so we used

those which were already adopted by other federal agencies.

(Slide.)

There are a few regulations and directives in the Department of Defense that provide for protection of human subjects, and I will get into each of those in a little bit more detail as we go.

The first one I will not speak much about. That is just the Department of Defense section of the Code of Federal Regulations that provides for the Common Rule in the Department of Defense. It is 32 CFR Section 219.

Title 10 of the U.S. Code, Section 980, Directive 3216.2, Directive 6000.8, and then the interim final rule for classified research are specific items that I would like to address in turn.

(Slide.)

The first is Title 10 of the U.S. Code, Section 980. This statute applies as far as I know exclusively to the Department of Defense among the federal agencies. Basically it says that funding that

is appropriated to the Department of Defense may not be used for human subject research unless the informed consent of the subjects has been obtained. It also allows a provision for under special circumstances that informed consent to be provided by a legal representative of the subject if the research is intended to be beneficial to that particular subject. That is Title 10, USC Section 980.

As I said, I do not believe that it applies to any other federal agency and here is where one of those opinions comes in that I offer the disclaimer for. I think that probably makes our program a little bit more stringent than maybe some of the others.

(Slide.)

This is our directive published in 1983 and, as I said, it was based upon the Common Rule that had been adopted by Health and Human Services in 45 CFR and by the Food and Drug Administration in 21 CFR. It applies to all Department of Defense components as well as to contractors and grantees which receive Department of Defense money to do human subjects

research.

(Slide.)

DOD Directive 6000.8 is really brand new. It just came out in 1999. There was a previous version of it but the new version just came out last year. Primarily it provides for the administration and funding of clinical investigation programs but there are two portions of it which I think make it especially important for the protection of human subjects in clinical investigation programs.

The first is which -- the first provision is that if a subject in a DOD sponsored clinical investigation program is injured or becomes ill as a result of participating in that program, they are guaranteed medical care following that injury or illness.

The second provision is that it prohibits any requirement for the subjects to sign a statement that would limit their right to compensation for any possible injury.

(Slide.)

I do not know if you are all aware of this particular issue or not but there is an interim final rule for protection of human subjects in classified research programs and, of course, the Department of Defense does some classified research involving human subjects.

We have finally in the Department of Defense become a signatory to the interim final rule. In fact, Secretary Cohen, the Secretary of Defense, just signed that last month and he also at the time that, he signed that he issued a policy letter to all Department of Defense components indicating that in conducting classified research projects with human subjects, they were to adhere to the provisions of the interim final rule.

(Slide.)

I have one slide to talk about implementation of our programs and policies and it is listed as an organizational chart but it is not necessarily intended to mean that everything flows down.

As with all matters in the Department of

Defense, the ultimate responsibility for the protection of human subjects resides with Mr. Cohen, the Secretary of Defense.

However, he has delegated that responsibility and authority to the Director of Defense Research and Engineering, Dr. Hans Mark, and my office within the Deputy Undersecretary of Defense for Science and Technology is under Dr. Mark's office, the Director of Defense Research and Engineering. So I am that little regulatory affairs block there.

Under Dr. Mark are the Secretaries of the Army, Navy and Air Force, and then the heads of the DOD components like the Joint Commands and Special Operations Command, and other defense agencies.

All of those, Secretary of the Army, Secretary of the Navy and Secretary of the Air Force have a staff at their Surgeon General's level, Surgeon General of the Army, Surgeon General of the Navy and Surgeon General of the Air Force, which provide a secondary review of human subjects research protocols and also provide for service specific policies for the

conduct of human subjects research.

The DOD components do not necessarily have -- well, do not have their own Surgeon General, so their protocols are generally secondarily reviewed by the Surgeon Generals of the services.

(Slide.)

I did not bring hard copies of the directives and I apologize for that. I suppose we can come up with them but I tried to save a few trees in the course of doing this but I would like to provide you with a web site at which any Department of Defense directive can be found.

I just learned yesterday afternoon too late to fix this unfortunately that this .mil extension may not be accessible to everyone. It may just be a military extension. If you try to log on to this and you are not able to, let me know in some way. We are going to publish all of the relevant Department of Defense directives on the web site of the Director of Defense Research and Engineering so they will be available to you as soon as we get that web site up

and running.

DR. CHILDRESS: That might be one of our recommendations.

DR. FORCINO: That might be. Take that for action. Thank you.

The other point on this slide is that the Department of Defense portions of U.S. Code and the Code for Federal Regulations are obviously in searchable databases that can be accessed on the web just by using the codewords United States Code or Code of Federal Regulations.

That concludes my presentation.

Thank you.

DR. SHAPIRO: Thank you very much.

DR. FORCINO: Yes, sir.

DR. SHAPIRO: Once again thank you very much and we are going to hold questions and see first of all if Ms. Rodriguez is here.

Thank you very much.

I am sorry. This is not Ms. Rodriguez. You are the substitute, Helene Deramond.

Ms. Helene Deramond, also from the Department, who will speak to us.

HELENE DERAMOND, DEPARTMENT OF EDUCATION

MS. DERAMOND: I have copies of Blanca Rodriguez's remarks for distribution.

DR. SHAPIRO: Perhaps staff could pass those around. Is there someone on the staff who could pass these around?

MS. DERAMOND: Thank you.

DR. SHAPIRO: Welcome.

MS. DERAMOND: Thank you.

The Department of Education has several protections for human research subjects in addition to the Common Rule that have evolved over time and that work together to, in fact, enhance the Common Rule protections.

The first three that I am going to mention are independent of the human subjects regulations and the last two are add-ons.

In 1974, the Federal Education Rights and Privacy Act was signed into law. It is often referred

to as the Buckley Amendment after its principal sponsor, Senator James Buckley of New York. It has been amended a total of six times over the past 26 years.

Basically what FERPA does is afford parents the rights to inspect and review their children's education records, the right to amend the records, to have the records amended, and to have some right of control over disclosure of the information.

It also provides that personally identifiable information from student records may be disclosed only after obtaining prior written consent of the parent, except in certain cases, and there are 14 exceptions enumerated in the statute.

Of particular interest to researchers is that one of the exceptions allows a school to disclose information without prior parental consent to an organization conducting certain studies for or on behalf of the school.

These rights transfer to the students when the student turns 18 or enrolls in a school of post-

secondary education.

FERPA applies to educational agencies that receive federal funds under any program administered by the Department of Education. So this basically covers all elementary and secondary schools and virtually all post-secondary institutions.

This regulation is administered by the Family Policy Compliance Office and the Office of Management. Ms. Rodriguez's office is in the Office of Grants Policy and Oversight.

In contrast to the Common Rule, it is a post-violation remedy. In other words, the investigations occur after a violation may have occurred rather than before.

PPRA, the Protection of Pupil Rights Amendment, also was initially introduced in '74 and it gives parents the rights to -- the right to inspect instructional materials in connection with research funded by the Department of Education. There were major amendments in 1978, the Hatch Amendment, which requires parental consent for certain types of surveys

issued to minor students. Surveys in seven particular areas that are -- and the seven areas are listed in the handout -- political affiliation, mental and psychological problems potentially embarrassing to the student, illegal, antisocial, self-incriminating and demeaning behavior, critical appraisals of other individuals, and so on and so forth.

It was amended again in 1994 to remove ambiguity in the laws and particularly to mean any survey, analysis or evaluation that elicits information from the seven areas, so it is a little bit broader than the Common Rule restriction to research.

It really affects all state education agencies, local education agencies, grantees, contractors using any funds from the Department of Education for surveys or studies that elicit information about children's attitudes, beliefs or habits.

Again, this regulation is administered by the Family Policy Compliance Office and this, too, is a

post-violation remedy and the thrust of this office has been to provide technical assistance and training to prevent violations from occurring.

We also have the confidentiality statute that has been in place since 1988 and it protects research subjects in a number of ways. It provides that the individually identifiable data collected by the National Center for Education Statistics in the Department of Education cannot be used for any purpose other than the statistical purpose for which they were collected.

Individually identifiable data are immune from the legal process and without the consent of the individual concerned, the individually identifiable data can now be admitted as evidence or used for any purpose and any action, suit or other judicial or administrative proceeding.

NCES can make the data available. However, it must strip it of personal identifiers or, if it cannot do so, because the material would not be of use to the researchers, it cannot release the data until

the researchers have signed a licensing agreement with the National Center for Education Statistics.

And the licensing agreement requires that the researchers protect the data. The penalties for violating the statute are severe. They include five-year jail terms and fines up to $250,000. And the confidentiality statute applies to the life cycle of the data from the time they are collected to the time they are destroyed.

The three regulation statutes I just mentioned are the ones that are independent of the Common Rule. The last two are add-ons. In 1991, the National Institute for Disability and Rehabilitation Research amended its program regulations to strengthen the IRB membership requirements that are found in the Common Rule.

Whereas, the Common Rule requires that consideration be given to including on the IRB persons who are knowledgeable about and experienced working with vulnerable subjects. The NIDRR IRB membership requirements state that the IRB must include

individuals concerned with the welfare of vulnerable subjects. It is "must," not “give consideration to.”

The history of that is that in 1980, the Department of Education had proposed several departures to the common policy, and at the last minute, in 1991, when it became clear that the department would not be able to be a cosignatory of the Common Rule, it dropped those departures and instead amended its program regulations.

This particular provision is administered both by the grants, policy and oversight staff and by NIDRR. We do look for the presence of persons that meet those requirements on the IRB, whether it be for a single project assurance or a multiple project assurance.

Finally, we have Subpart D, additional protections for children. You all know what the additional protections of Subpart D are. The rationale for the department's adopting the subpart was in part because the department does not have the flexibility that other agencies may have to adopt

policy without rule making, so we went through the formal rule making process. And then there was a very practical consideration.

Grantees that operate under a multiple project assurance already were required to comply with subpart D and we would have been in the awkward situation of having some research subjects less protected than others, not depending on the degree of risk, but on whether or not the research was being conducted on an SPA or an MPA.

And then, of course, children are the primary focus of the department's mission. Many of the research that the department sponsors does, in fact, include children.

This Subpart D is administered by the grants, policy and oversight staff.

To my right is Peter Wathen-Dunn, who is the counsel from the Department of Education, who advises Blanca Rodriguez on all issues pertaining to human subjects. He is very knowledgeable about the history, legislative history of many of these additional

provisions, and is here to respond to any questions that you may have.

DR. SHAPIRO: Thank you very, very much. Again thank you for coming here and being here this morning. I want to once again thank all the presenters this morning both from the Department of Defense, Department of Education and Veterans Affairs.

Let's now go to questions from commissioners for any one of the panelists.

Yes, Diane?

DISCUSSION WITH COMMISSIONERS

DR. SCOTT-JONES: I have a question about the Department of Defense regulations. You said that informed consent is required for all human subjects research. I want to make sure that I understand that. That means there are absolutely no exceptions, not even say for a survey where the identity remains anonymous and the participants -- there are no exceptions to the requirement of informed consent?

DR. FORCINO: Ma'am, my understanding is that there are no exceptions, but I probably will call in

my back ups just to confirm that if you do not mind.

DR. SHAPIRO: Please.

DR. LANE: That is true.

DR. MESLIN: You have to come to the mike.

DR. SHAPIRO: I apologize. For anyone else speaking, we have to speak through a microphone so our transcript gets created appropriately and accurately.

DR. LANE: That is very true. The regulation --

DR. MESLIN: Introduce yourself.

DR. LANE: Pardon me.

DR. SHAPIRO: You are?

DR. MESLIN: Introduce yourself.

DR. LANE: Oh. I am Ed Lane.

DR. SHAPIRO: His predecessor.

DR. LANE: Part 980 is very specific to DOD, where it does require informed consent for any research program, and there are certain instances where survey questions like you are talking about are deemed outside of that area but they are very complicated and generally general counsel has to get

into that.

The survey questions are used to enhance a program of something like a Tricare survey that would come out where they are asking specific questions about members that utilize a service, and Tricare being our health care program where they are asking generalized questions and it has gone through a whole panel and they have deemed that outside the necessity to use informed consent. Other than that, they have to get informed consent for all of our programs.

DR. SCOTT-JONES: Okay. I have another question. If you can answer this briefly from the Department of Defense and from Veterans Affairs, could you say briefly what kinds of research you do conduct? Can you -- is that something you can answer briefly?

DR. FORCINO: In very general terms, the Department of Defense conducts research in enhancing human performance in operational environments in its diving and aviation medicine and occupational health, as well as programs in infectious disease, programs in combat casualty care or trauma research to name a few.

DR. BURRIS: The Department of Veterans Affairs conducts research across really the whole spectrum from basic biomedical science to clinical trials to health services research. About 70 percent of our research is clinically focused and more than 98 percent of our research is in nine identified high priority health care needs of veterans, including aging, chronic diseases, military occupational exposures, mental health and substance abuse, and so on.

DR. SHAPIRO: Thank you.

Alex?

PROF. CAPRON: The first question is to the Veterans Affairs and the Department of Defense.

Since you both have programs which provide for some form of either compensation or care necessary to remedy a problem that has arisen in research, have you conducted any analysis of what the experience has been and were there any baseline data to compare what the experience was before you had such programs?

DR. BURRIS: We have not conducted an

analysis of what has occurred since the policy was put in place and I am not aware of baseline data.

DR. LANE: I would have to say that that would be the same for the Department of Defense. I am not aware of it if we have it.

PROF. CAPRON: Is this something which you believe you could report to us on? You have not studied it but there would be some database that would show how many people have been injured and in what fashion and what remedies were available to them as a result of your perspective programs?

DR. BURRIS: We certainly could survey our field research offices at the individual facilities to develop some information on that.

PROF. CAPRON: I do not know how we go about requesting such, but if it requires Dr. Shapiro to say that this is something we would like to have, I know for myself it is something --

DR. SHAPIRO: The general --

PROF. CAPRON: -- we would be interested in.

DR. SHAPIRO: The general area of

compensation for injury is one we are really quite interested in thinking through, and any data that you have available that you could share with us would be very much appreciated and would help us clarify our own thinking and so perhaps you could consult with whoever is necessary to consult with and just let us know. Perhaps you can let Dr. Meslin know whether that is possible and what kind of data is possible and so on and if we can be helpful we would certainly be glad to be helpful.

PROF. CAPRON: Then I have separate questions for the same two departments. Dr. Burris will not be surprised since I come from Los Angeles to be -- and I am quite concerned about the issue of the adequacy of the oversight for research conducted at veterans facilities. Rather than focusing on the problems that existed in the West L.A. VA, I wonder whether you would have now, or again be able to respond to this later, information that would be useful to us as to what you learned about how these kinds of problems arise in a system that has the level of oversight that

you describe and what steps you may have taken systemwide to ensure that those kinds of problems are not arising elsewhere and will not arise? I mean this in the positive sense. What did you learn from this about the adequacy of your own program and what steps are necessary to make it more adequate?

DR. BURRIS: What we learned from that experience was that the systems of oversight that we had in place were not adequate to give us a comprehensive view of the programs at our disseminated field operations and as a consequence of that we have instituted two new oversight mechanisms.

One being the external accreditation contract that I referred to, which will involve -- we anticipate will involve -- a site visit to each of our facilities that is engaged in research activities at least once every three years for a formal review of the -- not only the human subjects protection program but also to some -- well, I am sorry. We do have a separate accreditation program for the animal care activity. So this will focus on the human subjects

protections.

And the final details of that contract are not yet worked out. We are at the moment -- I have a stack of proposals on my desk for review by a panel, an internal panel. So we will have more information about that once the final details of the contract are negotiated and that is actually up and running.

The other major activity that we have instituted is the establishment of the Office of Research Compliance and Assurance, or ORCA, and I would like to, if I may, ask Joan Porter to come up and tell you just a little bit about what the plans are for that.

DR. PORTER: Thank you, Jim.

At present we have three persons in ORCA. We have plans to expand the organization greatly. We are working very closely hand in hand with the Office of Research and Development. It is currently carrying out the assurance and compliance responsibilities under the Common Rule.

We plan to have a headquarters office with

approximately eight persons emphasizing human subjects protections, animal welfare and research integrity.

As Jim mentioned, a centerpiece of our headquarters program will be an accreditation contract, and we will be inspecting each one of our sites at least once every three years.

In addition to that, we would like to have random site visits, and we anticipate having some site visits for cause, and are building into our budgets and administrative procedures those types of visits as well.

We had a brainstorming session last week in launching ORCA. ORCA is headed by Dr. John Mather, who is an M.D. And at our brainstorming session, we had ethicists come in to talk to us as well as persons from the various regions and field offices in the VA to talk about what they thought were priorities for ORCA and how we could work better with our field operations.

In addition to our field -- our headquarters office, we will have field offices. This year we will

have -- we will stand up five. Next year we will have six offices that will work with the individual sites with human subjects activities at the VA medical centers so it will be a rather large enterprise.

In our brainstorming session, we repeatedly emphasized the necessity for education and training, and for creation of an atmosphere in which people know what they are supposed to be doing and are encouraged and have incentives to do that. So we want to start out on a very positive note, and look for ways to prevent problems before they begin.

We are pretty excited about this. We all have a lot to learn, but I think we have a chance to make some real progress here and engage in leadership in the Department of Veterans Affairs and the protection of the human subjects and animal welfare in research integrity.

DR. SHAPIRO: Alex, you brought up the issue of West L.A. VA. I do want to indicate that I was out at a meeting in Chicago and forgive me for forgetting the name but there is a biannual meeting of the VA's -

- I do not know if it is research administrators. Anyway they met in Chicago a couple of months ago and I arrived early and attended a session which really was an analysis of what had happened at West VA.

I cannot -- I am sorry to say I cannot remember the names of the individuals who presented. It was an extremely thoughtful analysis, not defensive at all, and I thought they really had isolated the issues very, very thoughtfully.

I do not know whatever has happened to those particular perspectives in this process. I presume they are part of it, but I must say I was very impressed with their own self-analysis of it and how undefensive it was and how forward looking and progressive it was. I hope that will be reflected and I am sure it will be in the programs that you are carrying forward.

PROF. CAPRON: Actually, Mr. Chairman, I was going to ask if such sort of a root cause analysis had been done, because one could reason backwards from your response and say, well, if you are doing this,

this and this, you must have thought the problems were X, Y, Z but if the kind of description that our chairman just gave exists, if there are documents which could be shared, my question is: all the research institutions that have not yet had the kind of analysis that the VA has given to its own IRBs and its review process at its facilities where we know as little about what is going on there as you did before the problems arose, and I would love to see, particularly if the analysis has that kind of characteristic or flavor that the chairman describes, if it could be tracked down, whichever presentation this was, if it is something in writing or several reports, I realize there may be some things which are not documents because of personnel information that would be in them that are not disclosable to us probably, but if there are things which have a generalized analysis of what the causes were and how this arose, I think it would be very instructive for us as I suspect it would be for other departments but it is part of our charge to look at this.

If you could share that I would appreciate it.

DR. PORTER: We will try to pull together some information that would be helpful on lessons learned.

PROF. CAPRON: Yes. Good.

The question for Dr. Forcino or his predecessor who is here with us was we heard this morning from Dixie Snider about the ways in which public health activities do not always fit well under the heading of research although they share certain characteristics.

There have been criticisms mounted by people such as Dr. George Annas, Professor George Annas, about some of the activities which have been engaged with enlisted men in terms of the use of novel agents that may be responsible for problems, medical problems that have arisen, and the ways in which the department is not required in his description of things to treat those as research with all the kinds of informed consent protections that you described.

Can you shed any light on this? Are there ways in which the military situation is unique? Are there ways in which those programs are defined out of research? Are they, in fact, conducted as though they were research and there actually is informed consent and the descriptions to the contrary are mistaken?

DR. FORCINO: I will take a shot at this but will probably turn the microphone over to Dr. Lane before we are finished.

I am assuming that you are referring to cases in which, for example, investigational new drugs might be used for force health protection.

PROF. CAPRON: Yes.

DR. FORCINO: And there are cases obviously, some in the news right now, in which that takes place. There is an executive order, and there is a pending Department of Defense directive, to cover the use of investigational new drugs for forced health protection. It is not typically considered to be a research issue. It is considered to be a force health protection issue that is an operational issue.

PROF. CAPRON: I want to make sure I am understanding. You are saying "force" as in armed forces or "forced"?

DR. FORCINO: The armed forces.

PROF. CAPRON: So force health protection is a way of saying the protection of the servicemen in the forces.

DR. FORCINO: Correct.

PROF. CAPRON: Okay.

DR. FORCINO: I am sorry about that.

PROF. CAPRON: No, no. It is I just wanted to clarify that.

DR. FORCINO: There are provisions within the executive order and within the draft directive that provide for obtaining the informed consent of the service members if that is possible to do. You have to understand that in some military contingencies, things may happen so quickly that informed consent is not possible, and it is up to the Secretary of Defense to request from the President a waiver of the informed consent process under those circumstances.

PROF. CAPRON: And this is -- what you are describing is something that would be a new development, the particular rules that you are referring to.

DR. FORCINO: To my knowledge, this is a new development, yes.

PROF. CAPRON: And prior to that was such a process of informed consent or a presidential waiver of the requirement --

DR. FORCINO: I will have to ask Dr. Lane to answer that.

PROF. CAPRON: -- in place or could you proceed without that, the formal waiver?

DR. LANE: The article you are talking about is Title 10, Part 1107, which was just recently enacted and that does require essentially presidential signature to -- in order to use something that would be deemed beneficial by a large panel for the benefit of our men and women that might be in harm's way by some unknown agent and they might have an IND that would be useful for that purpose. And they can do

that without informed consent individually if they follow the directions of 1107.

PROF. CAPRON: Yes, I understand, but prior to that --

DR. LANE: Was there something -- prior to that, no, I do not think that there was and we tried to get informed consent when we could but we -- you talked about the bromide thing that came up and I think that this started the whole thing rolling to get some protections and requirements set into law to make that happen. It is the next step in doing it properly.

PROF. CAPRON: Well, I guess my puzzlement is since the presentation emphasized your statutory requirement, which is not, by the way, unique, under the 1974 Research Act, of course, all research has to be conducted with informed consent and IRB review if it is sponsored by the Federal Government, but your specific requirements which you emphasize required informed consent, and yet until this directive comes into effect, the use of an IND drug, that is to say a

drug which in nonmilitary settings would certainly go through an IRB and require all the protections thereof with informed consent was not the requirement. Is that my understanding? It is just seems --

DR. LANE: I cannot answer that. I do not know for a fact.

PROF. CAPRON: Well, I would like to have that clarified because it seems as though the heavy emphasis you put on the statutory requirement of informed consent and yet the fact that in order to protect the armed forces an IND substance could be used without informed consent and I guess without all the rigmarole that goes with that sounds as though there is a tension there that was resolved somehow by either saying we have some reason to override it because these are enlisted men and women or it is not research. It is like a gigantic --

DR. FORCINO: A partial clarification --

PROF. CAPRON: -- compassionate use exception and it is not research. We are just using it because we need to use it.

DR. FORCINO: To clarify what I had expressed in my presentation, I was addressing only the research and development aspects and not the use of investigational new drugs and, in fact, we -- to my knowledge, we do not consider the investigational new drugs for force health protection to be in the research and development domain and that is probably the reason that we are not understanding one another.

PROF. CAPRON: Well, no, I understand you but it is curious to say that something which is in an IND category and which would otherwise -- if you came to a university and recruited subjects, other 18 year old, 19 year olds to take this, you would go through a process that would involve informed consent and IRB review and so forth. But when you give it to service men and women you did not go through that process because you were intending to benefit them, I gather, and that is why I say it is like a gigantic compassionate use exception when you say we are taking it out of the research side.

I would be interested then to know did you

really not conduct research in the sense of keeping records of who got it, and what the apparent results of giving it to them? I would be surprised if that were the case.

I do not suppose that unit A got it and unit B did not, but maybe I am even wrong in that assumption.

DR. FORCINO: I think that neither of us really know if there were provisions prior to 1107 and prior to the executive order for protection of those forces.

PROF. CAPRON: Could we get some --

DR. FORCINO: We will attempt to do that.

DR. LANE: We will have to go to general counsel. One of the things that I would like to clarify, if you would not mind, you mentioned something -- I think that you were thinking about enlisted individuals versus the commission corps. There is no distinction.

PROF. CAPRON: I know. I used the term inelegantly.

DR. LANE: Okay. All right.

PROF. CAPRON: I did not mean enlisted versus the officers.

DR. LANE: Right.

PROF. CAPRON: Sorry.

DR. SHAPIRO: Rachel wanted to comment on this.

Rachel?

DR. LEVINSON: I can just clarify the situation for provisions that existed prior to the current one, which is that the Food and Drug Administration had issued an interim rule several years ago at the request of DOD to provide for an opportunity to administer investigational new drugs for protection of troops without informed consent to give a specific waiver that had been exercised twice.

And in the course of that, it may be that the IND that is issued is already approved for another use, so it may not be research in that particular sense. It would be considered off label use, for example, or it may not be approved for use, but that

that existed as an interim rule and that FDA wanted to move, and Bonnie Lee is here. She worked on that extensively and can give you details separately if you want them but there was a provision. It was interim.

There had been comments collected by FDA on perhaps revoking that opportunity and then in statute there was a requirement that DOD pursue a different policy through a presidential waiver where the president would grant that, and that is the basis for the executive order and the new rules that have been issued already.

DR. SHAPIRO: Okay. Thank you. I have a number of commissioners who want to speak.

Diane?

DR. SCOTT-JONES: I have a question of clarification. I am very interested in the special regulations for children and how they came to be adopted or not adopted, and in my notes from Duane Alexander's presentation to us I noted that the regulations for children were published in '74 and approved in 1983. That is quite a long time lag. But

then I look at the very nice document from the Department of Education and it states here that the Department of Health and Human Services approved Subpart D in 1991, an even longer time.

So I was wondering if there is anyone who could clarify when they were adopted by Health and Human Services. I do not know if Dr. Ellis needs to answer that one.

MR. WATHEN-DUNN: Well, they were in effect. All that I was saying was when they came out and did their remake of the -- along with the Common Rule they amended a lot of their other subparts to make them consistent with changed numbering and whatnot in the Common Rule. And so they did have to make amendments to -- in '91 to Subpart D. All we are saying is that Subpart D in its current shape has been in existence since '91.

By the way, I am Peter Wathen-Dunn.

DR. SHAPIRO: Thank you.

MR. WATHEN-DUNN: Office of General Counsel for the Department of Education.

DR. SHAPIRO: Thank you.

DR. SCOTT-JONES: Okay. So is it correct that they were first approved in '83 and then there is a somewhat amended version that was approved in '91, is that right?

MR. WATHEN-DUNN: That is correct.

PROF. CAPRON: In '83 the Department -- in '83 D was still with HHS that is to say.

MR. WATHEN-DUNN: That is right.

PROF. CAPRON: I mean, there was not a separate Department of Education at the time so there would have been no separate --

DR. SCOTT-JONES: That is what I mean.

MR. WATHEN-DUNN: Well, in '83 we were separate.

PROF. CAPRON: You were just separated that year.

MR. WATHEN-DUNN: 1980 we became a separate agency. As a matter of fact, we were participating, when we were still the "E" in HEW, in extensive discussions about what specific rules should apply to

educational research that were incorporated into their adoption of amendments to their Subpart A and also Subpart D although we did not comment as directly on the Subpart D things at that time.

DR. SHAPIRO: Rhetaugh?

DR. DUMAS: This one is for Dr. Forcino.

Years ago I became aware that there was a program within the DOD for extramural breast cancer research. Is that program still a part of the DOE?

DR. SHAPIRO: DOD.

DR. FORCINO: DOD.

DR. DUMAS: DOD, I mean.

DR. FORCINO: Yes, I believe it is.

DR. DUMAS: Okay. One of the things that I have been concerned about, it seems so odd in relation to the mainstream concerns of the Department of Defense to have a program for breast cancer research and also there was some talk about research on prostate cancer.

I wondered how the DOD handles the concerns about the protection of human subjects for these

programs. Are there special rules, regulations? Are they a part of the mainstream rules and regs for the DOE (sic)?

DR. FORCINO: I think --

DR. DUMAS: I am sorry. I keep making that mistake.

DR. FORCINO: That is quite all right.

DR. DUMAS: DOD.

DR. FORCINO: I think there are probably two questions there. The answer to the first one is that although subjects like the breast cancer and prostate cancer may not seem to be force readiness issues primarily, occasionally additional funds are added to our budget by the Congress for specific things, and the breast cancer and prostate cancer are two such issues.

The second question is that generally the funds for those programs are distributed on a competitive basis to performers who provide protocols to the Department of Defense, to the executive agent for those areas, and they are to my knowledge

administered as any other money is administered that is provided to the Department of Defense, that is the same provisions apply but I will ask Dr. Lane to confirm that.

DR. LANE: That is correct.

DR. DUMAS: Thank you.

DR. PORTER: May I comment briefly?

DR. SHAPIRO: Yes.

DR. PORTER: The Congressionally mandated research programs are handled primarily by the U.S. Army Medical Research and Material Command. They include breast cancer, prostate cancer, neurofibromatosis research or for veterans illnesses research, and they are -- there is a large office of human subjects protections and animal welfare at the USAMRMC.

They are reviewed by the Department of Defense, the Army IRB, as well as the IRBs at the sites where the awards are given out under the provision of the Common Rule.

DR. DUMAS: Very good. Thank you.

DR. SHAPIRO: Larry?

DR. MIIKE: For the Department of Education, during your presentation you made some comment to the effect that when it became clear we could not sign on to the Common Rule we went -- can you expand on that?

MR. WATHEN-DUNN: The Department of Education had been participating in the development of the rule and going to many, many meetings. In fact, which were in large measure conducted and facilitated by Joan Porter at that time and they -- the Assistant Secretary for Education -- excuse me, for Special Education and Rehabilitative Services was concerned that with a number of problems that she saw in the regulations that were being proposed, and she had a list of ten concerns that she sent to the group.

Unfortunately, the group had gone quite a bit a way down the track on developing the policy and considering what changes would need to be made to the HEW rule/HHS rule to make it something that would be used as the Common Rule.

And so there was a whittling down process,

and finally the Assistant Secretary was insistent that these two matters be included and that is that for IRBs that are reviewing research involving persons with mental disabilities or children that the IRB consist -- must include a person who is not just an expert in conducting research and understanding the risk there but that they be -- include a person who is an advocate for the special needs of either the disabled -- the mentally disabled or for children.

And there was -- most of the -- virtually unanimous result. All the other agencies opposed the inclusion of that because they felt that the general standards for composition of the IRB were sufficient and that it did require them to consider whether the needs of certain people be on the IRB as a general matter as they reviewed things and also provided that if the IRB needed to consult with additional people they could do that in reaching their decisions and so they felt that that was a necessary -- that the needs -- the changes proposed by the department were unneeded.

The Assistant Secretary did not agree, and I think that she was influenced at that time at least in part by the fact that Subpart D was not going to be part of this promulgation of the initial Common Rule.

So there was essentially a two-and-a-half to three year standoff between the Department of Education and the other agencies and OSTP and HHS which was spearheading the regulation.

Eventually through some informal discussions, the Assistant Secretary agreed to relent on that, and instead put those special protections only in the regulations of our research office for which it was appropriate in the Department of Education and as a result we agreed to sign off on the Common Rule and in that regard the Assistant Secretary felt that it would be inappropriate to hold it further because the regulations did add protections generally for research that had not been in existence for the department prior to that and so that is how the issue was resolved.

DR. MIIKE: Just to follow up that. To make a long story short and I heard -- I cannot remember which other agencies, but you have the Common Rule and then you have add-ons by specific departments so that is essentially what you did.

MR. WATHEN-DUNN: That is what we did. As a matter of fact --

DR. MIIKE: Why couldn't you have done that earlier on?

MR. WATHEN-DUNN: We had no rules to amend at that time. We did not even have -- unlike HHS, which had a regulation protecting human subjects, we had no rule at all. So we had to sign on and get the Common Rule promulgated to have those protections so we could not on our own do it in advance especially when there was an initiative to get all the agencies to sign on together to a Common Rule.

DR. MIIKE: No, I understand, but what I am saying is why not just sign the Common Rule and then at the same time add your special --

MR. WATHEN-DUNN: That is essentially what we

did.

DR. MIIKE: Yes, but it took three-and-a-half years.

MR. WATHEN-DUNN: Yes. Well --

DR. MIIKE: So I understand, but he was very reluctant to sign off on them. Okay. Thank you.

DR. SHAPIRO: Thank you.

Any questions from the commission?

Marjorie, you have a question?

DR. SPEERS: Yes. I had two questions. One is for the Department of Education. Among the five rules, guidance and amendments that you presented today, can you distinguish between which ones have, if you will, have the force of law or regulations and which ones do not and how you implement -- what are the mechanisms you have for implementing these various policies?

MR. WATHEN-DUNN: Do you want to answer the first one?

MS. DERAMOND: FERPA and PPRA are administered by the Family Policy Compliance staff.

The office does receive complaints and investigates the complaints.

DR. MURRAY: Please move your microphone.

MS. DERAMOND: Okay.

DR. MURRAY: Thank you.

MS. DERAMOND: The office investigates complaints and provides technical assistance and training to prevent violations from occurring in the first place. That is with PPRA and FERPA. The NCES statute is administered by the National Center for Education Statistics. The penalties -- as I understand them -- are quite a deterrent. There have been no formal complaints although there have been some concerns expressed. Is that correct, Peter?

MR. WATHEN-DUNN: That is correct.

MS. DERAMOND: Correct.

The Subpart D and the NIDRR IRB membership requirements are administered by the Grants, Policy and Oversight staff in conjunction with the program offices. As we review grant applications or contract proposals and before the funding -- before the awards

are made.

MR. WATHEN-DUNN: And those are all in regulations.

MS. DERAMOND: They are.

DR. SPEERS: May I ask one more?

DR. SHAPIRO: Absolutely.

DR. SPEERS: One more question.

Part of what the commission will be looking at is the -- if I can say the utility of having a Common Rule and so I want to pose this question to the three agencies but in particular would like DOD to comment on this question.

Which is given that DOD has had a parallel human subjects protection system what influence has the Common Rule had on human subjects protection within DOD? What has changed as a result of having signed on to the Common Rule?

DR. FORCINO: I am not sure that I am in a position to answer that. Again I am going to ask Dr. Lane to handle that question, please.

DR. LANE: I am not sure I can answer it

myself.

DR. SPEERS: Because the question is not clear or do you need me to expand on it or --

DR. FORCINO: No.

DR. SPEERS: Okay.

DR. FORCINO: I think the question is clear. I simply do not know the answer.

DR. SPEERS: Okay.

DR. SHAPIRO: Thank you.

Alex?

PROF. CAPRON: You described just now from the Department of Education perspective the investigations where there are complaints. Those relate to an IRB process or to particular research?

MR. WATHEN-DUNN: The FERPA and PPRA are requirements in the Department's General Education Provisions Act and we have an office that promulgated regulations telling educational agencies and institutions what they had to do to comply with the act. And the department relies on individuals to come to it with complaints if they believe the educational

institutions are not complying with the procedures and the requirements of either of those two Acts.

So it is a post-fact sort of analysis and the responsibilities of the office that reviews those complaints is to determine whether there is -- the offices have -- the educational institutions, have they, in fact, violated the rules in FERPA or PPRA and, if so, what actions they have taken to correct the error and whether there is an adequate assurance that they will comply with the regulations in the future.

So unlike the IRB procedures there is not an advanced review of research or consent things. Now, of course, FERPA and PPRA are much narrower in what they address. PPRA addresses the seven issues that are included in that statute but there is a great deal of overlap.

PROF. CAPRON: Well, you just described them as narrow. In a way from a research perspective I would say they are broad in the sense that most of what they deal with has nothing to do with research.

It has to do with the special areas of sensitivity under the PPRA or protection of privacy issues having to do with school records. Is that correct?

MR. WATHEN-DUNN: Yes, but they require consent before you can do those things and in many cases what you will find is there are certain things that are being done by educational agencies which if they had been done by somebody in university A, B, C and they wanted to do a survey it would look very much like research.

But the school is doing them to determine statutory compliance and so there is a great deal of confusion in that area about where one ends and where another begins, and so you have to look at the facts of each case to determine whether it is just a PPRA issue or whether it is also a human subjects issue.

PROF. CAPRON: And this begins to look very much like the questions of program evaluation and surveillance that we were hearing from CDC this morning.

MR. WATHEN-DUNN: I am sorry I was not here

for that presentation.

PROF. CAPRON: Well, it is a description of the difficulty. I think you were here this morning.

MS. DERAMOND: Yes, I was.

PROF. CAPRON: Would you agree that it is the same sort of issue? I am sure it is not identical. But surveillance, what is happening with the program or evaluating the program --

MS. DERAMOND: There are similarities. For example, school districts for the purposes of planning a drug prevention program may need to survey students to determine the extent of the problem. Is it research or is it just a needs assessment? And where the Common Rule leaves off then PPRA takes over if it is a required survey of the kids to determine the extent of need.

PROF. CAPRON: And in how many cases have you in the last decade, say, had to do evaluations or investigations, whatever you call them, because of complaints about something which was not being treated as research and maybe should have been?

MR. WATHEN-DUNN: The office -- I cannot speak to those kinds of numbers and I am not sure that the office necessarily has those kinds of distinguishing data available to them. They do, do a number of complaints. More of their complaints are actually just under the privacy provisions of FERPA than under the PPRA statute.

Certainly we could go back and see if they can determine anything about that but I am not sure that they really have any reliable data that could speak to that issue.

DR. SHAPIRO: Thank you. Any further questions?

Alta, do you have any questions?

PROF. CHARO: No, I am fine over here. Thank you.

DR. SHAPIRO: Okay. Thank you.

Yes, Ms. Porter?

DR. PORTER: I always have one more thing to say, I guess, but I did want to make two points. First, to Alex Capron.

Alex, the Presidential Advisory Committee on Gulf War Veterans Illnesses did a rather extensive analysis of the effect of the interim final rule of FDA and the waiver of informed consent in military exigencies, and I would commend to you that report for a review of the history and the implications of that interim final rule.

I did want to say that our Office of Research and Development and the Office of Research Compliance and Assurance, ORCA, intends to work quite closely with our National Ethics Committee and our Director of the National Ethics Center, and Ellen Fox is here today sitting over here. So we want to work in a larger context in our attempts to ensure protection of human subjects in the Department of Veterans Affairs.

DR. SHAPIRO: Thank you very much.

PROF. CAPRON: Can I ask the Eric Cassell question? That is to say has your --

DR. SHAPIRO: You have to ask Eric if you can ask it.

PROF. CAPRON: Has your center, your

bioethics center, which I believe is based -- is that the one in Seattle you are referring to?

No?

DR. PORTER: Ellen, would you like to comment?

PROF. CAPRON: Not the internal office but don't you have a contracted office?

DR. FOX: Is this on?

DR. SHAPIRO: I do not think that works.

DR. FOX: The National Center for Ethics is at White River Junction, Vermont.

PROF. CAPRON: Vermont.

DR. FOX: But I am the director of that center and I am Washington headquartered.

PROF. CAPRON: Yes. Has that center engaged in educational activities on the IRB issues with your in-house IRBs at the veterans centers?

DR. FOX: The center has not historically had that as its major focus but we are moving more in that area and we are working very closely with ORCA and with the Department of Research and Development to

move towards that and so we are increasing our efforts in that area.

PROF. CAPRON: You have not done it yet.

DR. FOX: We have done some, but not on a system-wide basis very comprehensively.

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

Well, thank you all very much. I very much appreciate your responsiveness to the questions and your presentations.

I would like to draw this morning's meeting to a close. I just want to remind the commissioners -- yes, Tom?

DR. MURRAY: I have one request as we think more broadly. Not about today's session.

DR. SHAPIRO: Right.

DR. MURRAY: But it was inspired by the last two days.

DR. SHAPIRO: Right.

DR. MURRAY: And actually by comments more specifically that you made and Alex made, the

specifics which I cannot recall, but I know the general point I want to make.

If we set about defining what counts as research, if we wish to decide what is a reasonable protection for the subjects of research, all of which I think are valuable enterprises, to me it would be helpful in going back as it were to sort of first reasons and asking what is this class of activities in which various individuals, scientists, clinicians, public health professionals, et cetera, interact with persons such that we think they have particular moral weight and require specific kinds of publicly sponsored and overseen protections?

I mean, I think there is -- so maybe research is not the right word. I do not think conflict of interest is the only reason but I would just like to step back and revisit that.

One way to get into it was helped in the past two days by thinking more about the history and learning more about the history of how it is that we got interested in the first place. The history does

not tell us why we ought to be interested, but it does give us some insight into how it is that we came to frame things the way we did and how it might be useful in the future to reframe them a bit to pick up on new activities like public health research and other things that we are learning about.

So that is my note. I would love to have in the report a visiting of the history but an effort to really rethink almost from the start what it is we think we are concerned with.

DR. SHAPIRO: Thank you very much. That is very useful and very much I think what Alex had in mind when he made his comment and I very much support that idea.

Again I do want to remind commissioners that on your way back to home base if you have any comments on the international materials that were in the agenda please get them to Eric or Ruth as soon as possible and with respect to what I would call in our own vocabulary the comprehensive project, the oversight of federal regulations and so on for protection of human

subjects. We will be increasing the intensity of our communications between meetings on these issues as we begin formulating questions and/or recommendations like Larry and I think Eric mentioned.

And it is very helpful to us to get some response. Not when you get a big raft of information but when you get some well-formulated questions so it can help us prepare materials that you really will find satisfactory at the next meeting.

We also have a very crowded meeting in February. We will be consulting with commissioners to see if it is possible to extend that commission by half a day and it may not be possible. We will have to check with everybody's schedules and so on, but you will be receiving some communication to that effect and we will see what is possible for that.

Any other issues before we adjourn?

Eric?

DR. CASSELL: Well, would you put on the internet or in e-mail the dates of the meetings you would like us to attend if possible?

DR. SHAPIRO: Yes. You are talking now about the meetings that are occurring around the country?

DR. CASSELL: Yes. Just dates and places and so forth.

DR. SHAPIRO: Right. Right. That is right. We have some just general indication. We will get you specific information, which is not -- it is not specific. It is a date and so on in the materials presented. We will do that. Thank you.

Okay. Well, thank you all very much. We are adjourned.

(Whereupon, the proceedings were adjourned at 11:41 a.m.)

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