HUMAN SUBJECT RESEARCH PROTECTIONS

HEARING

BEFORE THE

SUBCOMMITTEE ON CRIMINAL JUSTICE,
DRUG POLICY, AND HUMAN RESOURCES

OF THE

COMMITTEE ON
GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

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HUMAN SUBJECT RESEARCH PROTECTIONS

WEDNESDAY, MAY 3, 2000

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON CRIMINAL JUSTICE, DRUG POLICY,
AND HUMAN RESOURCES,
COMMITTEE ON GOVERNMENT REFORM,
Washington, DC.

The subcommittee met, pursuant to notice, at 2:36 p.m., in room 2247, Rayburn House Office Building, Hon. John L. Mica (chairman of the subcommittee) presiding.

Present: Representatives Mica, Cummings, and Kucinich.

Staff present: Sharon Pinkerton, staff director; Steve Dillingham, special counsel; Don Deering, congressional fellow; Lisa Wandler, professional staff member; Ryan McKee, clerk; Alex McKinnon, intern; Cherri Branson, minority counsel; and Earley Green, minority staff assistant.

Mr. MICA. Good afternoon. I'd like to call this hearing of the Subcommittee on Criminal Justice, Drug Policy, and Human Resources to order. I apologize for the delay. There is a full committee hearing going on at this time, but with the consent of the minority, we are going to proceed.

We have two panels today, and we do want to finish this hearing this afternoon. It is an important hearing, entitled "Human Subject Research Protections," one of which I'm pleased to work with my colleague Mr. Kucinich, the gentleman from Ohio, and this is the second hearing we've conducted on this matter.

I am going to start with the regular order of business. We may at some time have to recess for a vote, either in committee or on the floor, but we'll proceed with opening statements, recognizing myself first and then the gentleman from Ohio.

This hearing before the Subcommittee on Criminal Justice, Drug Policy, and Human Resources will examine a critical problem for which reforms have been recommended by the Office of Inspector General [OIG], to the Department of Health and Human Services [HHS]. Last December, we conducted a hearing on this topic in New York City where past issues had surfaced regarding the protections of persons participating in human research projects. The December hearing also coincided with revelations regarding the tragic death of 18-year-old Jesse Gelsinger of Tucson, AZ. Jesse died just 4 days after being injected with a cold virus and engineered genes. Researchers were shocked and a national debate ensued on gene therapy experiments and the reporting of adverse effects. The National Institutes of Health [NIH], issued a solicitation to the medical community requesting help.

Even in today's Washington Post, I read that there were reports of more deaths which were not reported to authorities and which also put more lives at risk. The question I pose today is whether HHS heeded this cry for help and has that agency acted promptly to prevent future tragedies.

Our December hearing included testimony from both OIG and also from HHS. At that time, it was apparent that HHS had not implemented the Office of Inspector General recommended reforms for protecting human research subjects.

Today, we'll revisit this important issue. We will hear in fact that more deaths of participants in human research have been reported, and that, in fact, more violations of required human subject protections have been revealed. The Office of Protections Against Research Risk [OPRR], is one component of the HHS agency with special responsibilities for protecting human research subjects. The Food and Drug Administration [FDA], is another. Apparently neither has received the support and commitment from the administration and the Health and Human Services Secretary that is needed; indeed, that is required to enhance the protections for research subjects.

Furthermore, the Department continues to putter around with this important issue, virtually ignoring most of the sound OIG recommendations and dragging their feet.

Why is HHS so reluctant to act proactively in reforming its programs and increasing the protections for those participating in research? That's a question we have to ask today. What justification is there for continued delays? From the evidence supplied to date, the answer is not likely to prove comforting, especially as human research projects multiply and new research frontiers emerge. Protecting the lives of those involved in research should be foremost in HHS thinking, research practices and also in its regulatory priorities.

Last December, this subcommittee asked the question, what actions are being taken to reduce unnecessary health and safety risks to human subjects? We should receive an answer today better than that given to us last year, which was an admission that practically nothing had been done. According to the most recent OIG report, however, it appears that not much has changed from our last hearing. I think there's a bipartisan agreement that this inaction is unacceptable.

The June 1998 recommendations of OIG appear both in my opinion reasonable. They're also urgently needed and generally propose strengthening the Institutional Review Boards [IRBs], that approve and oversee human research projects. The OIG made the following recommendations and observations relating to IRBs. First, they said they face major changes in the research environment. They also said they review too much too quickly. Furthermore, they said they conduct minimal continuing review of approved research. They face conflicts that threaten their independence. They provide little training for investigators and board members and neither the IRBs nor HHS devote much attention to evaluating IRB effectiveness, and again, these are some of the points that were raised about the IRBs.

The Office of Inspector General recommended reforms in some of the following areas: First, Federal requirements such as performance evaluations; second, strengthen protections, including enhanced IRB monitoring; third, educational requirements, including educating IRB members; fourth, preventing conflicts of interest and also the question of broadening representation on IRBs; fifth, reducing IRB workloads, and sixth, improving Federal oversight, including IRB registration.

To date, the responses by HHS have indeed been most disappointing. The latest OIG report findings include, and let me cite them, first of all, minimal progress has been made in recasting Federal IRB requirements so that they grant IRBs greater flexibility and hold them more accountable.

Another of these findings stated, minimal progress has been made in strengthening continuing protections for human subjects participating in research.

Another finding, no educational requirements have been enacted for investigators or IRB members.

Another recent finding here is that there has been no progress in insulating IRBs from conflicts that can compromise their mission in protecting human subjects, and we heard testimony about some problems in this area in our last hearing.

Another more recent finding and update tells us that minimal progress has been made in moderating workload pressures of the IRBs.

And finally, minimal progress has been made in reengineering the Federal oversight process.

All of these really are disappointing to the subcommittee and me, particularly after our last hearing. We thought we would see some additional actions in some of these areas.

As indicated in our previous hearing, HHS annually invests approximately $5 billion of its research dollars in approximately 16,000 research projects that involve human beings. To provide oversight for these research projects, OPRR has agreements with more than 4,000 federally funded institutions, each with an IRB. Under OPRR guidelines, research subjects must be fully briefed on the purpose, the duration and the procedures of the research project before agreeing to participate. OPRR has the authority to investigate and require corrective action and suspend funding to an institution.

Last month, it was reported in the Los Angeles Times that specialists overseeing a clinical trial of the diabetes drug Rezulin did not follow the required procedures for monitoring a volunteer who died after taking the medication. Less than 10 days ago press reports announced the death of a 42-year-old Massachusetts woman participating in a drug study sponsored by the Nation's top medical research agency. She died after receiving the wrong kind of blood.

As we'll hear today, the OPRR has acted to suspend research at a growing number of universities where research requirements have been violated. What is required to convince HHS to take additional needed actions to prevent more harms and also to save more lives? While I'm glad to hear that some improvements are underway, I don't think that the agency can truthfully testify here today

that in fact enough has been done or is being done. If it does, we should consider placing this responsibility elsewhere.

I take no joy in holding another hearing on this topic within 5 months of the previous hearing, but if inaction continues in the face of mounting dangers and death, we may need further oversight hearings and further investigation into this. We also may have to work with the Appropriations Committee and some of the other committees to put some caveats on spending this significant number of dollars, some $5 billion, in research that involves human subjects, and we'll look at those options.

I thank the witnesses who have come before us today to testify. We appreciate your willingness to appear before this subcommittee and to share your knowledge and experience as we strive to address this urgent public health priority. Time is of the essence in this matter, and further delay must be avoided.

I'm pleased again to have the cooperation on this issue and active participation and leadership of the gentleman from Ohio. Let me recognize Mr. Kucinich at this time for his opening statement.

[The prepared statement of Hon. John L. Mica follows:]

OPENING STATEMENT

Chairman John L. Mica

Subcommittee on Criminal Justice, Drug Policy and Human Resources

May 3, 2000

Why the Delays in Protecting Human Research Subjects?

This hearing before the Subcommittee on Criminal Justice, Drug Policy and Human Resources will examine a critical problem for which reforms have been recommended by the Office of Inspector General (OIG) to the Department of Health and Human Services (HHS). Last December, we held a hearing on this topic in New York City, where past issues had surfaced regarding the protections of persons participating in human research projects. The December hearing also coincided with revelations regarding the tragic death of 18-year old Jesse Gelsinger, of Tucson, Arizona. Jesse died just four days after being injected with a cold virus and engineered genes. Researchers were shocked, and a national debate ensued on gene-therapy experiments and the reporting of adverse effects. The National Institutes of Health (NIH) issued a solicitation to the medical community requesting help. Even today, the Washington Post reports more deaths which were not reported to authorities, putting more lives at risk. The question I pose today is whether HHS heeded this cry for help, and has acted promptly to prevent future tragedies.

Our December hearing included testimony from both the OIG and HHS. At that time, it was apparent that HHS had not implemented OIG recommended reforms for protecting human research subjects.

Today, we will revisit this important issue. We will hear that more deaths of participants in human research have been reported, and that more violations of required human subject protections have been revealed. The Office of Protections Against Research Risks (OPRR), is one component of HHS agency with special responsibilities for protecting human research subjects; the Food and Drug Administration (FDA) is another. Apparently neither has received the support and commitment from the Administration and the HHS Secretary that is needed -- indeed that is required -- to enhance protections for research subjects. Furthermore, the Department continues to putter around with this important issue, virtually ignoring most of the sound OIG recommendations.

Why is HHS so reluctant to act proactively in reforming its programs and increasing protections for those participating in research? What justification is there for continued delays? From the evidence supplied to date, the answer is not likely to prove

comforting -- especially as human research projects multiply and new research frontiers emerge. Protecting the lives of those involved in research should be foremost in HHS thinking, research practices and regulatory priorities.

Last December, this Subcommittee asked the question: What actions are being taken to reduce unnecessary health and safety risks to human subjects? We should receive an answer today better than that given last year, which was an admission that practically nothing had been done. According to the most recent OIG report, however, it appears that not much has changed. I think there is bipartisan agreement that this is unacceptable.

The June 1998 recommendations of the OIG appear reasonable and urgent, and generally proposed strengthening Institutional Review Boards ("IRBs") that approve and oversee human research projects.

The OIG report made the following observations regarding IRBs:

- "They face major changes in the research environment"
- "They review too much, too quickly"
- "They conduct minimal continuing review of approved research"
- "They face conflicts that threaten their independence"
- "They provide little training for investigators and Board members"
- "Neither IRBs nor HHS devote much attention to evaluating IRB effectiveness"

The OIG recommended reforms in the following areas: 1) federal requirements (such as performance evaluations); 2) strengthened protections (including enhanced IRB monitoring); 3) educational requirements (including educating IRB members); 4) preventing conflicts of interest (e.g., broadening representation on IRBs); 5) reducing IRB workloads; and 6) improving Federal oversight (e.g., IRB registration).

To date, the responses by HHS have been most disappointing. The latest OIG report findings include [see pages 2-3][emphasis added]:

- Minimal progress had been made in recasting Federal IRB requirements so that they grant IRBs greater flexibility and hold them more accountable.
- Minimal progress has been made in strengthening continuing protections for human subjects participating in research.
- No educational requirements have been enacted for investigators or IRB members.
- There has been no progress in insulating IRBs from conflicts that can compromise their mission in protecting human subjects.
- Minimal progress has been made in moderating workload pressures of IRBs.
- Minimal progress has been made in reengineering the Federal oversight process.

As indicated in our previous hearing, HHS annually invests approximately $5 billion of its research dollars in approximately 16,000 research projects that involve human subjects. To provide oversight for these research projects, OPRR has agreements with more than 4,000 federally funded institutions, each with an IRB. Under OPRR guidelines, research subjects must be fully briefed on the purpose, duration and procedures of a research project before agreeing to participate. OPRR has the authority to investigate and require corrective action, and suspend funding to an institution.

Last month, it was reported in the Los Angeles Times that specialists overseeing a clinical trial of the diabetes drug Rezulin did not follow required procedures for monitoring a volunteer, who died after taking the pill. Less than ten days ago, press reports announced the

death of a 42 year-old Massachusetts woman participating in a drug study sponsored by the nation's top medical research agency. She died after receiving the wrong kind of blood.

As we will hear today, OPRR has acted to suspend research at a growing number of universities where research requirements have been violated. What is required to convince HHS to take additional needed actions to prevent more harms and to save more lives? While I am glad to hear that some improvements are underway, I don't think that the agency can truthfully testify that enough is being done. If it does, we should consider placing this responsibility elsewhere.

I take no joy in holding another hearing on this topic within five months of a previous one. But if inaction continues in the face of mounting dangers and deaths, we may need further oversight and hearings.

I thank the witnesses who have come to testify today. We appreciate your willingness to appear before this Subcommittee and to share your knowledge and experience as we strive to address this urgent public health priority. Time is of the essence in this matter, and further delay must be avoided.

Mr. KUCINICH. Thank you very much, Chairman Mica, and I want to especially commend you for calling this hearing and for your continuing efforts to demonstrate your dedication to the protection, the health and the welfare of the American public in clinical research trials. I think this Congress is fortunate to have your leadership in this area.

I'd like to thank the witnesses for testifying regarding the Inspector General's report on the protection of human research subjects. I'll begin by saying that I am disappointed in the lackluster response to the recommendations as the Inspector General's report finds, but I am not surprised. The state of Federal and local human research subject protections has been lacking for quite some time. The subject has only been highlighted in the past couple of years due to high profile cases with respect to gene therapy that have prompted Federal inquiries on the oversight of human research protections. However, I believe that human research protections extends far beyond the narrow scope of gene therapy. All aspects of human biomedical research must be monitored and everyone must be protected from risks involved in medical experimentation.

The Inspector General's report in 1998 I believe outlined specific changes that could be made to improve the current protections in place. However, the current IG report indicates that the Department of Health and Human Services has done little to implement these recommendations, enacting only two. With respect to recommendations on oversight and protections by Institutional Review Boards, the report states that, "minimal progress has been made in strengthening continuing protections for human subjects participating in research." Regarding Federal oversight it states that, "minimal progress has been made in reengineering the Federal oversight process. Federal oversight of IRBs is not equipped to respond effectively to the changing pressures and needs of the current system of protections." Well, this is unacceptable.

The Federal Government provides funds for a vast complex of experiments that involve human subjects. More than $16 billion per year in Federal funds are used for such research. Some 20,000 experiments at more than 4,000 universities, hospitals and other institutions are involved. Duke University alone has $175 million per year in Federal research grants. The lives of tens of thousands of people are at stake along with the reputation and integrity of very important research institutions.

The Federal Government's system to monitor these institutions and ensuring the safety of human research subjects continues to be outdated, ineffective, underfunded and understaffed. The only bright spot in this dismal area of Federal activity is the positive efforts being made by the Office of Protection from Research Risk under the direction of Dr. Gary Ellis. In spite of the lack of funds, lack of staff and enormous institutional pressures, Dr. Ellis continues to make progress in the monitoring and investigating of research institutions which conduct human experimentation. His work on behalf of the American public should be commended and recognized.

I know that I as well as the subcommittees will want to be apprised of the office's ongoing investigations. I look forward to hearing from you in the future. I am glad we have representatives here

from HHS who will be able to address the Inspector General's report. I look forward to hearing your testimony.

Thank you very much, Mr. Chairman.

Mr. MICA. I thank the gentleman and there being no further opening statements at this time we're going to proceed with our first panel as the order of business. The first panel today consists of George Grob, and he is the Deputy Inspector General for Evaluation and Inspections at the Office of Inspector General, Department of Health and Human Services.

The second witness is Dr. William Raub, and he is the Deputy Assistant Secretary for Science Policy of the Office of the Secretary of Health and Human Services.

We have also accompanying these two witnesses Dr. Mark Yessian, who's the Regional Inspector General for Evaluation and Inspections in the Department of Health and Human Services. we have Dr. Gary Ellis, Acting Director of the Office of Protection from Research Risks.

We have Daniel Michels, and he is the Director of Enforcement of the Office of Regulatory affairs at the Food and Drug Administration.

This is an investigation and oversight subcommittee of Congress. We will swear you in in just a minute. All of our witnesses appear under oath. Furthermore, if you have any lengthy statements or documentation you'd like to have made part of the record, upon request through the Chair and with the concurrence of the minority that will be granted. Those are basically the rules and the way we'll proceed today.

At this time let me confer. Without objection Mr. Kucinich has moved that the record be left open for additional comments or submissions for 2 weeks. So ordered.

Mr. KUCINICH. Thank you, Mr. Chairman.

Mr. MICA. And we now will proceed and I'll ask our witnesses if they'd stand and be sworn.

[Witnesses sworn.]

Mr. MICA. The witnesses answered in the affirmative. We'll now hear first from the Deputy Inspector General for Evaluations and Inspection, George Grob. He has submitted rather lengthy findings for the subcommittee and Mr. Kucinich moves without objection that they be made part of the record. So ordered. So we will have your complete testimony in here. We'd like each of our witnesses today to try to limit their presentations, oral presentations, to 5 minutes if possible. I know we have two that are making presentations I think with this panel, and we will submit any additional data or testimony upon request.

With that, let me recognize George Grob, Deputy Inspector General for Evaluation and Inspections. You're recognized, sir.

STATEMENTS OF GEORGE GROB, DEPUTY INSPECTOR GENERAL FOR EVALUATION AND INSPECTIONS, OFFICE OF INSPECTOR GENERAL, DEPARTMENT OF HEALTH AND HUMAN SERVICES; MARK YESSIAN, PH.D., REGIONAL INSPECTOR GENERAL FOR EVALUATION AND INSPECTIONS, DEPARTMENT OF HEALTH AND HUMAN SERVICES; WILLIAM RAUB, PH.D., DEPUTY ASSISTANT SECRETARY, SCIENCE POLICY, OFFICE OF THE SECRETARY, HEALTH AND HUMAN SERVICES; GARY ELLIS, PH.D., ACTING DIRECTOR, OFFICE OF PROTECTION FROM RESEARCH RISKS; AND DANIEL MICHELS, DIRECTOR OF ENFORCEMENT, OFFICE OF REGULATORY AFFAIRS, FOOD AND DRUG ADMINISTRATION

Mr. GROB. Thank you, Mr. Chairman and Mr. Kucinich.

The system which was designed to protect the human subjects of research has inherent vulnerabilities, most of which remain even after the best efforts of our Department to address them. To understand why this is the case we must go back to its origins.

The protections were gradually developed after the Second World War in response to research atrocities that came to light during the Second World War and other troublesome research experiments that arose shortly thereafter. In 1966 the Surgeon General issued a human subject policy for the Department of Health, Education and Welfare, and in 1974 the National Research Act required reviews by Institutional Review Boards for all research sponsored by the Department of Health, Education and Welfare. In 1991 those procedures were adopted by 15 other Federal Departments in what has come to be known as the Common Rule.

These and other developmental events during that period were among the prouder days of American science with respect to protection of human subjects. However, during this same period research exploded in size and complexity and numbers, in amounts of money spent. The Institutional Review Boards were overwhelmed and left behind. Vulnerabilities subtly emerged, at first unnoticed. Lately we've begun to notice them.

In 1998, at the request of the Food and Drug Administration, we conducted a study of the unauthorized marketing of investigational medical devices, and during the course of this report we stumbled upon some problems with the Institutional Review Boards and other systems designed to protect the human subjects of this research. For example, in one experiment the researcher was authorized to implant 75 investigational devices for surgery, and reported to the Investigational Review Board that 37 had been implanted. We found that 264 had in fact been implanted.

We found other discrepancies in the surgery reports of other investigators: 15 devices were implanted during the 6-week period in which the research had been suspended by the Institutional Review Board; we found changes not made to the research protocols requested by the board and reported as having been made; we found informed consent forms missing, in some cases consent forms obtained after the surgery was performed and other similar results.

As a result of stumbling upon these kind of findings, we decided that a more systematic look was required at the Institutional Review Boards and others systems designed to protect human subject research, and based on that work we published in June 1998 a

more comprehensive review that provided an early warning of troubles and vulnerabilities in the system. To get a better sense of the problems that the institutions were facing at the time let me just rattle off some of the circumstances that made it more difficult for them to do their jobs.

When they began this work in the sixties and seventies most research consisted of research at a single site. Today it's mostly multi-sites across the country, sometimes even the world. It used to involve a single investigator. Now it involves hundreds of investigators. It used to be a small cohort of subjects. Now it's thousands. Most funding came from government offices. Now a lot of it comes from commercial sponsors. A lot of it used to be done at teaching hospitals. Now it's done at clinics, doctors offices and in other settings.

There's been a rise of patient consumerism and demands for access to investigational procedures, drugs and devices, and new types of research have emerged.

In 1978 there were about 500 institutions with Institutional Review Boards. Now there is somewhere between 3,000 and 5,000 of them. They used to review an average of 43 proposals a year. Now it's up to about 300. Adverse event reports are flooding their offices, in some cases being stored in boxes on the floor without being reviewed. In one case we found a couple of hundred of these reports coming in per month at one of the Institutional Review Boards.

With such a change in circumstances, the Institutional Review Boards were not able to keep up. They had insufficient resources. They have been unable to stay on top of the research that's being performed so that while they might give a review of the proposals before the research starts, they can seldom look beyond that. We found insufficient training, little evaluation and oversight, and we made corresponding recommendations which have already been cited in the opening statements.

Recently the Department has attempted to deal with these problems and has taken a number of steps which Mr. Raub will summarize for you. I particularly want to point out the stepped up enforcement that NIH has been doing. Recently 10 onsite visits were made and seven institutions had their research suspended. I think the sentinel effect of these efforts has been very strong and has sent a wave through the research community indicating that improper practices will not be tolerated.

But fundamental vulnerabilities remain and we're reminded too often of the consequences of this. I know that Departmental officials are engaged in attempting to address these vulnerabilities and our own work is continuing, but I would like to add to my statement here a note that the solutions don't depend entirely on the Department. The companies which sponsor research, the investigators, the universities and medical centers, their Institutional Review Boards—they're all involved and they're responsible too. Their talent, energy, creativity and dedication is what fueled the boom in research that overwhelmed the human subject protection system. These same forces now need to be directed to bring it back into balance.

[The prepared statement of Mr. Grob follows:]

Testimony
Before the Committee on Government Reform
Subcommittee on Criminal Justice, Drug Policy and Human Resources
United States House of Representatives

Protecting Human Subjects:
Status of Recommendations

Statement of
George Grob
Deputy Inspector General for Evaluation and Inspections

May 3, 2000

Office of Inspector General
Department of Health and Human Services

For Release on Delivery
Expected at 2:00pm
Wednesday, May 3, 2000

Good afternoon. I am George Grob, Deputy Inspector General for Evaluation and Inspections, in the Office of Inspector General (OIG), U.S. Department of Health and Human Services. I am pleased to testify at today's hearing on the Department's responses to our June 1998 report on the Institutional Review Board system for protecting human subjects of medical research.

Mr. Chairman, the Department has taken a number of promising steps, but few of our recommended reforms have been enacted.

Our June 1998 Report on Institutional Review Boards

Background. In June 1998, we released a series of reports on the Federal system for human-subject protections centers on institutional review boards (IRBs). This broad-based review was initiated after a 1995 OIG study, requested by the Food and Drug Administration (FDA), raised significant concerns about the adequacy of subject protections and the IRB system. The report focused on medical device research and found, for example, that in one instance that an investigator had implanted 264 investigational devices when he only had approval for 75 implants. We found another investigator had not gotten informed consent from the subjects and yet other instances in which changes in the informed consent documents that IRBs had requested were not incorporated. Another investigator

moved from the city of practice without informing the subjects of his clinical trial who to report to after he was gone.

Findings. In the broad 1998 report, we warned that the effectiveness of IRBs was in jeopardy. We found that the clinical research environment had changed in the 20 years since the system was first established and the changes have had significant implications for IRBs. IRBs were becoming overwhelmed by their workloads, lacking necessary resources to keep up and becoming pressured to do more in a shorter time frame and with limited information on many trials. They provided little training to investigators and Board members regarding principles and practices of human subject protection. Of particular significance, they conducted very little oversight of clinical trials once the trials had started. In addition, Federal oversight of protections was limited, leaving Department with little sense of how well IRBs were actually doing their job.

These findings led us to present numerous recommendations to the National Institutes of Health (NIH), its Office for Protection from Research Risks (OPRR), and the Food and Drug Administration (FDA). Brief summaries of both our findings and recommendations from the June 1998 report are attached to this testimony.

A Follow-up Report

Based on the continued interest in human-subject protections and a request from this subcommittee, we recently issued a follow-up report providing an accounting of how fully our 1998 recommendations have been enacted. We drew on information obtained over the past two years from Department officials and pertinent documents, data reported to us by the NIH and FDA, and interviews with Department officials who also provided comments on a draft of this report, many of which are reflected in the final. Let me state that this report is not a further examination of the adequacy of the Federal oversight of human subject protections or of the protections themselves. Instead, we used as a starting point our prior recommendations and provide an accounting of how fully they have been carried out. Attached at the end of this testimony is a table compiling each recommendation and a brief description of what, if any, action has taken place.

The Department has taken action and initiated several promising steps.

Increased Enforcement. Since June 1998, both OPRR and FDA have significantly stepped up their on-site presence at research institutions. Between April 1997 and May 1998, OPRR had conducted an on-site investigation at only 1 institution. Between June 1998 and March 2000, it conducted on-site investigations at 10 institutions. Since June 1998, OPRR also conducted off-site investigations (document reviews) at more than 140 additional

institutions. It found performance problems at a number of institutions it investigated and has required 7 of them to suspend some or all of their federally funded research. Where OPRR found weaknesses in the institutions' systems of protections, it cited institutions for substantive, broad-based deficiencies—ones that have direct consequences on the rights and safety of research subjects.

FDA's number of routine on-site investigations of IRBs increased from 213 in Fiscal Year 1997, to 253 in FY 1998, and 336 in FY 1999. The Center for Devices and Radiological Health, for example, issued eight warning letters to IRBs during FY 1999, compared to zero in FY 1998. The Center for Drug Evaluation and Research took administrative action against eight IRBs during FY 1998 and 1999.

Sentinel Effect. OPRR's oversight activities, in particular, have drawn the attention of the research community to issues of human-subject protections. The reviews at prominent medical centers, including the temporary suspension of federally funded research at 7 centers, have had a ripple effect beyond the individual institutions visited by OPRR. Many major medical journals and newspapers have given prominent attention to OPRR's enforcement actions. The adequacy of IRB oversight has been a topic at a number of national conferences and association meetings.

New Organization. In July 1999, the Secretary announced the relocation of OPRR from NIH to the Office of the Secretary and plans to establish a new advisory committee on protection from research risks to provide scientific and ethical guidance to the office. These actions, although not yet complete, have been widely publicized and are being taken to strengthen the stature and effectiveness of OPRR in its oversight role and are indicative of the Secretary's commitment to strengthening subject protections.

Other Initiatives. The Department has enacted two of our recommendations--as of October 1998, FDA now informs sponsors and IRBs associated with an investigator when FDA finds evidence of misconduct on the part of clinical investigator; and in June 1999, NIH issued a policy stating that all data and safety monitoring boards associated with NIH trials are expected to forward summary reports of adverse events to IRBs. Both actions are significant. For example, the summary information is key to an IRB's ability to ensure the continued safety of subjects. Both agencies have also increased their education outreach and resources. They have ongoing deliberations on additional proposed changes.

But overall, few of our recommended reforms have been enacted.

Despite these positive steps, there are still need for additional reforms. What follows is a brief description of any the Department actions taken in response to our six broad

recommendations. A table attached to this testimony provides a quick snapshot on the status of the Department responses.

Flexibility and Accountability

We called for the Department to lessen specific procedural requirements that add questionable of value and to require that IRBs undergo regular performance-focused evaluations. Beyond one concrete action discussed below, there have been few enacted reforms along the lines we recommended. Little has been done to grant IRBs more flexibility or to establish a Federal basis for assessing the effectiveness of IRBs.

In November 1998, FDA and NIH/OPRR jointly issued new regulation expanding the categories of research that may be reviewed by IRBs through an expedited review procedure. There are also active deliberations by an NIH Advisory Group geared towards reducing regulatory burden and streamlining processes for grantee institutions. Among its recommendations, the group proposed a change, about to be implemented, to the requirement that IRBs review all protocols before funding decisions are made, an improvement we suggested.

The most notable development around IRB performance evaluations is in the private sector. A private group devoted to the ethical conduct of research, is working to develop

performance standards and apply them as part of an accreditation process. Both NIH/OPRR and FDA are participating in these discussions.

Oversight of Ongoing Research

We made several recommendations to strengthen continuing protections of clinical research subjects after the research has begun. For example, we called for more explicit policies on when and how data safety and monitoring boards could be used in certain research trials and a suggested a requirement that they share summary information with IRBs. We also called for FDA to inform IRBs when it takes action against an investigator under the IRB's purview and to establish a requirement that sponsors and investigators notify IRBs of any prior IRB review of research. Finally, we called for increased IRB awareness of on-site research practices.

As stated earlier, FDA now informs sponsors and IRBs about investigator misconduct and NIH issued a policy requiring its data and safety monitoring boards (DSMBs) to forward summary information to IRBs. But, neither NIH nor FDA has issued requirements for sponsors to notify IRBs of prior reviews, nor have they issued guidance to IRBs to increase their attention to on-site research practices. FDA has not set forth regulations regarding the appropriate use for or composition of DSMBs, which can help provide and assemble valuable information for IRBs.

FDA requires all sponsors of gene transfer research, and sponsors overseen by the Center for Devices and Radiological Health, to routinely submit monitoring plans. But both of these policies do not address a large majority of clinical trials. We urge FDA and NIH take similar initiatives directed at other research areas.

Education and Training

We called for the Department to require institutions receiving Public Health Service Act funds establish an education program for investigators and that IRBs be required to educate their members. No Federal regulations have been enacted requiring institutions to establish education programs for clinical investigators. Similarly, no Federal requirements have been enacted calling for education for IRB members.

NIH intramural researchers are required to complete a web-based tutorial in order to conduct human-subjects research on campus. We urge NIH to consider expanding this policy to all extramural researchers, who conduct the majority of research funded by NIH. Both NIH and FDA have increased their educational outreach through numerous training presentations and seminars for IRBs and professional groups. NIH has constructed a website containing bioethics resources and has launched new training grants in subject protection issues and bioethics. FDA is in the process of updating its Information Sheets, an important source of IRB guidance. NIH/OPRR hired a full-time educational staff person in January 1999, and is in the process of further expanding this staff.

Conflicts of Interest

We called for a number of steps to mitigate the potential influence of conflicts on IRB reviews such as a requirement increasing the number of nonscientific and noninstitutional members on IRBs and a prohibition on equity owners of independent IRBs from participating in the IRB review process. We did not identify any significant action in the Department to mitigate potential IRB conflicts of interest. We continue to regard this as a significant area warranting attention. In the increasingly commercialized research environment, potential for conflicts within research institutions loom larger than ever and it is ever more important that IRB reviews be sufficiently independent, both in reality and in appearance.

Workload Pressures

We called for OPRR to hold institutions accountable for the resource commitments they made in their assurances and for FDA to modify its site visit protocol to more readily identify situations in which limited resources may jeopardize subject protections. OPRR's enforcement efforts have brought attention to IRB resource shortages at individual institutions. However, no further action has been taken to develop indicators of adequate resource levels or to enable greater investments to support IRB functions.

One approach that NIH reports is under consideration, and is worthy of attention, would be to allow institutions to allocate an additional increment of grant funds to provide necessary

resources for IRBs. A well-supported IRB should be considered a necessary cost of doing business.

Reengineering Federal Oversight

We called for NIH to revamp its oversight and assurance process and for FDA to revamp its on-site inspection process. We also called for the Department to require IRBs to register before being allowed to review research under the Department jurisdiction.

OPRR's and FDA's response in increasing their enforcement efforts is significant, as we have already indicated. By increasing their presence in research institutions, they have fostered compliance with Federal regulations there— and most likely at others as well. But neither body has yet enacted any significant revamping of their oversight processes as we have called for. This is unfortunate because stepped up enforcement without a more efficient, performance-oriented enforcement process will still leave us with an oversight system that falls well short of its potential.

FDA has substantially increased its IRB inspections, but it has not engineered any significant changes in its approach to these inspections. The inspections remain narrow and focused on procedural compliance, not results. NIH/OPRR reports that it has been developing plans to streamline the assurance process as we called for in our June 1998 report. But no actual change has taken place to date.

It is important to note that FDA has formed a working group to establish an IRB registration system. The working group has agreed upon specifications for this registry that reflect many of our suggestions. However, nothing has been implemented yet. We encourage the group to follow through with this effort.

The Common Rule: A Significant Barrier to Departmental Progress

The HHS core regulations concerning IRBs and human-subject protections are the basis of a common Federal policy on human-subject protections. The Federal policy, known as the Common Rule, is adhered to by the Department and 16 other Federal agencies.

Because any changes to the Rule call for the concurrence of all 17 Federal agencies, we must acknowledge that the reality of gaining concurrence among 17 Federal agencies inhibits a timely and effective the Department response to a number of our recommendations.

Several of our recommendations can be carried out through administrative changes, for example requiring education through contract and grant language or altering the assurance or inspection processes. However, other recommended changes, are subsumed in the Common Rule. A requirement, for instance, for more extensive representation on IRBs of nonscientific and noninstitutional members or stronger requirements on IRBs having

sufficient independence, could be difficult to carry out without the agreement of the other 16 agencies.

The intention of having a common Federal policy on human subject protections is an important one. One set of standards fosters a level of consistency in protections of human subjects in many different areas of research and makes complying with Federal regulations easier for researchers and sponsors. However, with the clinical research environment changing rapidly, we believe it is essential for the Federal policy and regulatory actions to keep pace. Therefore, legislative change may be necessary to achieve a timely implementation of many of our recommendations.

The Need for Action on a Broad Front

Our June 1998 inquiry and continuing work in this area convinces us that IRBs alone cannot do the job; other parties in the clinical research process, including sponsors and investigators, must take responsibility for subject protections. That is why, for example, our recommendations include actions that call for investigator education. Investigators, while they are in a position to do the most harm to patients, are also in a position to do the most good. More explicit Federal guidelines on recruiting subjects and the use and composition of data safety and monitoring boards can also help. The National Bioethics

Advisory Commission is also likely to offer further guidance in the near future on the kind of changes that need to be made in the Federal regulatory system.

New Opportunity for Leadership

The Department has a significant new opportunity to exert Federal leadership in protecting human subjects with the new office in the Office of the Secretary and a new advisory committee on subject protection issues. We urge that the new office give significant attention to our prior recommendations. We also urge that it continue the *important* enforcement efforts undertaken by OPRR over the past 2 years. The NIH/OPRR efforts have served as a reminder to research institutions, sponsors, individual investigators, and IRBs that the reviews must still be substantive in order to ensure adequate protections for human subjects. In the important quest to reduce regulatory burdens, it is important not to lose sight of this underlying protection function.

Both FDA and NIH will retain significant statutory and operational responsibilities for protecting human subjects despite the impending establishment of a Departmental office for subject protections. FDA still has the most visible on-site presence and thus is in the best position to identify shortcomings and opportunities for improvement. NIH retains significant roles in ensuring human-subject protections as a major sponsor of clinical research and as a conduit to the research community.

Conclusion

We continue to support the recommendations we made in our earlier report and call for a greater sense of urgency in carrying them out. They offer actions that would strengthen human-subject protections without impeding vital clinical research. They reflect a respect for the largely collegial manner in which IRBs operate. Yet, they also recognize that verification and accountability must also be important features of a system intended to protect human subjects.

Our recommendations are not a complete blueprint for action. In the months ahead, we will be conducting further inquiry that more closely examines how the Department oversight can enhance human-subject protections.

Thank you for the opportunity to testify on this most important topic. At this time, I would be happy to answer any questions which you or the other members of the Subcommittee may have.

The Effectiveness of IRBs Is in Jeopardy.

They Face Major Changes in the Research Environment. The current framework of IRB practices was shaped in the 1970s in an environment where research typically was carried out by a single investigator working under government funding with a small cohort of human subjects in a university teaching hospital. In recent years, that environment has been changing dramatically as a result of the expansion of managed care, the increased commercialization of research, the proliferation of multi-site trials, new types of research, the increased number of research proposals, and the rise of patient consumerism. Each of these developments has presented major disruptions and challenges for IRBs. "Never before," concluded one recent review, "has such a pressure-cooker atmosphere prevailed within the IRB system."

They Review Too Much, Too Quickly, with Too Little Expertise. This is especially apparent in many of the larger institutions. Expanded workloads, resource constraints, and extensive Federal mandates contribute to a rushed atmosphere where sufficient deliberation often is not possible. At the same time, the IRBs frequently are hard-pressed to gain access to the scientific expertise they need to reach informed judgments about the research taking place under their jurisdiction.

They Conduct Minimal Continuing Review of Approved Research. In the environment described above, continuing review often loses out. Even where there is the will, there often is not the time to go beyond the perfunctory obligations. A lack of feedback from other entities that oversee multi-site trials contributes to the problem. The result is that IRBs have all too little information about how the informed consent process really works and about how well the interests of subjects are being protected during the course of research.

They Face Conflicts That Threaten Their Independence. Clinical research provides revenue and prestige to the institutions to which many IRBs belong. The institutions expect IRBs to support these interests at the same time that they protect human subjects. The resulting tension can lessen the IRBs' focus on their basic mission. The minimal "outside" representation that typically exists on IRBs deprives them of an important counterbalance to the institutional interests. For independent IRBs, the dependence on revenue from industry sponsors exerts similar possibilities for conflict.

They Provide Little Training for Investigators and Board Members. The IRB system depends heavily on research investigators' commitment to uphold human-subject protections. But as that system now operates, it offers little educational outreach to investigators to help them become informed and sensitized about these protections. Similarly, it provides minimal orientation and continuing education for IRB members—a deficiency that is especially detrimental to nonscientific and noninstitutional members.

Neither IRBs Nor The Department Devote Much Attention to Evaluating IRB Effectiveness. IRBs rarely conduct inquiries to determine how well they are accomplishing their mission; their judgments of effectiveness rely mainly on the number of protection lapses or complaints that are brought to their attention. The Department agencies conducting oversight seldom go any further. The Office for Protection from Research Risks, in the National Institutes of Health, focuses almost entirely on up-front assurances. The Food and Drug Administration relies on compliance-focused inspections.

RECOMMENDATIONS

Institutional Review Boards: A Time for Reform
(OEI-01-97-00193), June 1998

1. Recast Federal Requirements So That They Grant IRBs Greater Flexibility and Hold Them More Accountable for Results.

▸ *Eliminate or lessen specific procedural requirements that are of questionable value.* Our aim was to provide overburdened IRBs with greater discretion that would enable them to develop more innovative and strategic approaches to their reviews. There are requirements, for example, that limit what IRBs can accomplish in conducting protocol reviews outside of convened board meetings. In addition, we highlighted requirements that call for IRBs to conduct full, annual reviews of approved protocols and that call for complete reviews of Federal funding applications prior to funding decisions.

▸ *Require that IRBs undergo regular performance-focused evaluations that are carried out in accordance with Federal guidelines.* In our review, we were struck by how little attention Federal oversight bodies and IRBs themselves gave to evaluating how successful IRBs were in protecting human subjects. It is time, we concluded, for the Federal government to mandate self-evaluations or, better yet, evaluations conducted by independent, outside parties. We also urged that the results of such evaluations be made public.

2. Strengthen Continuing Protections for Human Subjects Participating in Research.

▸ *Require Data Safety Monitoring Boards (DSMBs) for certain high-risk and multi-site trials.* DSMBs are independent assessment bodies that provide medical, scientific and other expertise that typically is not available on IRBs, thereby serving an invaluable function in protecting human subjects. We recommended that NIH and FDA take the lead in seeing that DSMBs become more firmly established as oversight mechanisms and become more clearly accountable.

▸ *Require DSMBs to provide summary information to IRBs.* We urged that DSMBs provide their summary assessments of adverse event reports to IRBs. IRBs are swamped with individual adverse event reports from multi-site trials, but these reports lack the essential context to confer meaning about the relative safety of the trial. DSMBs can provide this context and thereby enhance the IRB's capacity to assess ongoing safety.

▸ *Alert IRBs to corrective actions taken against investigators under the board's purview.* Although FDA provides information on its website about corrective actions that result from investigator inspections, the Agency does not routinely inform the respective IRBs of such actions. We recommended that FDA inform individual IRBs when it takes corrective action against an investigator who is conducting research reviewed by the IRB.

▸ *Require sponsors and investigators to notify IRBs of any prior IRB review of a research plan.* Sometimes sponsors shop around for an IRB that will give their protocol a favorable review. We pointed out that such action can undermine the IRB review process and, accordingly, urged that this requirement be enacted.

▸ *Call for increased IRB awareness of on-site research practices involving human subjects.* IRBs are rarely aware of what actually takes place between investigator and subject. We called for IRBs to move beyond their focus on the informed consent document and periodically check for themselves how the actual consent process is working. For particularly sensitive or risky projects, we suggested they might call for the participation of

counselors, ombudsmen, or other third parties that could be available to make certain that the consent process functions in the interest of human subjects.

3. Enact Federal Requirements That Help Ensure That Investigators and IRB Members Are Adequately Educated About and Sensitized to Human-Subject Protections.

- *Require institutions to establish an education program for investigators in human-subject protections.* Such a requirement exists for research involving animal subjects. We found the case for education requirements no less compelling for research involving humans. The mandatory education we called for could be provided through media such as seminars, individual instruction, videos, or on-line tutorials.

- *Require investigators receiving funding under the Public Health Service Act for research involving human subjects to provide a written attestation indicating that they will uphold Federal policies concerning human-subject protections.* We recommended such an attestation as a way of heightening investigators' awareness of their responsibilities as investigators and interest in participating in educational programs addressing human-subject protections.

- *Require IRBs to educate their members about human-subject protections.* In order for IRBs to adequately review research protocols to ensure human-subject protections, each board member must be educated in both applicable Federal regulations and ethical principles. We called for a specific mandate that IRBs and their parent institutions provide initial and continuing education.

4. Help Insulate IRBs from Conflicts That Can Compromise Their Mission in Protecting Human Subjects.

- *Require more extensive representation on IRBs of nonscientific and noninstitutional members.* At present just one IRB member can wear both of these hats and satisfy the requirement. We found that to be an untenable situation, one that can deprive IRBs of a valuable counterbalance to internal, institutional pressures that can threaten their independence.

- *Reinforce to IRBs and their parent institutions the importance of IRBs maintaining sufficient independence.* It is particularly important that IRBs not report to a part of an institution responsible for bringing in research funds.

- *Prohibit equity owners from participating in the IRB review process.* Such a practice does not necessarily inhibit the independence of the review process, but it establishes a situation that can undermine a perception of impartiality. We recommended that it should be disallowed.

5. Recognize the Seriousness of the Workload Pressures That Many IRBs Face and Take Actions That Aim to Moderate Them.

- *Require that IRBs have access to sufficient resources to adequately carry out their duties.* Our recommendation was directed not only to staff and board member resources, but also to space, computers, and other essential elements. We urged OPRR to hold institutions accountable for the resource commitments they made in their assurances and for FDA to modify its site visit protocol so that it could more readily identify situations where resource shortages jeopardize an IRB's ability to oversee research.

6. Reengineer the Federal Oversight Process

- *Revamp the NIH/OPRR assurance process.* NIH/OPRR's oversight process has been concentrated on reviewing up-front assurances aimed at obtaining an institution's commitment to adhere to Federal requirements. We found that assurance process to be paperwork-laden with little effect on IRB functioning. We urged that NIH/OPRR reorient the assurance process so that it rests on an institutional attestation to conform to Federal requirements, and then devote more NIH/OPRR resources to periodic performance-based reviews of institutions and their IRBs.

- *Revamp the FDA on-site inspection process.* We recognized that FDA has a much greater on-site presence than NIH/OPRR, but urged that FDA transform its site visit protocol from a narrow compliance orientation to one that is much more performance-based. Such an approach would pay particular attention to how individuals were actually being approached about participating as human subjects and to how IRBs were making risk-benefit trade-offs.

- *Require IRBs to register with the Federal government.* We found that one of the major impediments to Federal oversight of human-subjects research is that there is no complete registry of the IRBs reviewing this research. Such a registry would be invaluable for FDA and NIH/OPRR as it would allow them to target their oversight and communicate more effectively with IRBs.

Current Status of FDA and NIH/NIH/OPRR Response to Recommendations

Institutional Review Boards: A Time for Reform **(OEI-01-97-00193), June 1998**

Recommendation		Status
1. Recast Federal Requirements	**1a. Eliminate or lessen some of the procedural requirements**	▸ FDA and OPRR issued more expedited review categories (11/98) ▸ OPRR/NCI proposed demonstration project using a central IRB to streamline processes
	1b. Require IRBs undergo regular performance-based evaluations	▸ No action ▸ Private accreditation movement initiated
2. Strengthen Continuing Protections	**2a. Require Data Safety Monitoring Boards (DSMBs) for certain trials**	▸ NIH reasserts policy on appropriate monitoring of its trials (5/98) ▸ No other action
	2b. Require DSMBs to provide summary information to IRBs	▸ NIH requires its DSMBs to share summary info. with IRBs (6/98) ▸ No other action
	2c. Alert IRBs to corrective actions taken against investigators under their purview	▸ FDA now notifies IRBs and sponsors of actual and potential misconduct by clinical investigators
	2d. Require sponsors and investigators to notify IRBs of any prior review	▸ No action
	2e. Call for increased IRB awareness of on-site research practices	▸ No action
3. Enact Educational Requirements	**3a. Require institutions to establish an education program for investigators in human-subj. protections**	▸ NIH has launched a number of initiatives and OPRR has required the establishment of education programs as a result of investigations ▸ No action towards a requirement
	3b. Require investigators provide a written attestation to uphold human-subj. protections	▸ No action
	3c. Require IRBs to educate their members about human-subj. protections	▸ No action ▸ FDA and NIH/OPRR have required the establishment of educ. programs as a result of investigations and are active in outreach
4. Help Insulate IRBs from Conflicts That Threaten Their Independence	**4a. Require more extensive representation of nonscientific and noninstitutional members**	▸ No action
	4b. Reinforce the importance of IRBs maintaining sufficient independence	▸ No action
	4c. Prohibit equity owners from participating in the IRB review process	▸ No action
5. Recognize Workload Pressures	**5. Require that IRBs have the resources to adequately carry out their duties**	▸ No action
6.Reengineer Federal Oversight Process	**6a. Revamp NIH/OPRR assurance process**	▸ NIH has initiated a proposal to streamline the assurance process
	6b. Revamp FDA on-site inspection process	▸ FDA has increased its on-site presence, but no other action
	6c. Require IRBs register with the Federal gov.	▸ FDA set working group for registration process, but no action yet

Mr. MICA. Thank you. Does that conclude your opening statement?

Mr. GROB. Yes, thank you.

Mr. MICA. Let me now recognize, if I may, Dr. William Raub, who's the Deputy Assistant Secretary for Science Policy, the Office of the Secretary of Health and Human Services. You're recognized, sir. Welcome.

Dr. RAUB. Good afternoon, Mr. Chairman and members of the subcommittee. I am William Raub, Deputy Assistant Secretary for Science Policy at the Department of Health and Human Services. I am accompanied today by Gary Ellis, Director of the NIH Office for the Protection of Research Risks, and Daniel Michels, Director of Enforcement at the Food and Drug Administration. Thank you for this opportunity to testify regarding the protection of human research subjects.

For more than 50 years HHS and its predecessors have led the Nation and the world in protecting human research subjects from unnecessary risks. Our approach is rooted in the Nuremberg Code, whose principles have been adopted, reinforced and built upon in a succession of policies culminating in the current Federal regulations governing research with human subjects. HHS led the way in developing the core of these regulations, the so-called Common Rule, which has been promulgated by 17 different departments and independent agencies. In addition, FDA has carefully tailored its regulations for the product oriented clinical research it oversees so that they harmonize with the Common Rule.

The primary foci for implementing these regulations are the Institutional Review Boards [IRBs]. They are responsible for reviewing proposed research protocols and associated informed consent statements before subjects are recruited and clinical research begins. No covered project may commence without IRB approval. Further, IRBs are responsible for continuing review, that is, oversight of approved research projects throughout their life cycle. If in the course of continuing review the responsible IRB were to find cause for concern regarding the safety of research subjects, the IRB could halt the project temporarily or permanently or otherwise require the investigators to take whatever protective or corrective actions it deems appropriate.

Two types of IRBs exist: IRBs operated by research institutions such as academic health centers and IRBs that operate as private entities. Two HHS components share responsibilities for overseeing IRBs, the OPRR and the FDA. OPRR oversees IRBs operated by HHS awardee institutions. FDA oversees IRBs that review clinical research related to the products it regulates, irrespective of whether that research is ongoing at HHS awardee institutions or other sites.

HHS is very concerned that the effectiveness of IRBs is in jeopardy. Although the Inspector General's investigation did not reveal either significant instances of actual harm to research subjects or evidence of any widespread pattern of outright IRB failure, we must not let that be cause for complacency. Many IRBs face unacceptably large workloads with too little time and too few resources to do their job properly. The fact that instances of actual harm to research subjects have been few and far between is a credit to the

extraordinary dedication and prudent decisionmaking of IRB members and the commitment of investigators to the integrity of their work.

In the wake of the June 1998 reports by the Inspector General, OPRR and FDA stepped up the pace of their inspections. Taken together, their findings reinforce the conclusion that the IRB system is under considerable strain. Moreover, for several institutions the OPRR and FDA inspections led to partial or complete suspension of clinical research at those sites until the institution's deficiencies were corrected, often only after major revamping of the IRB structure and commitment of substantial additional resources by the research institutions. These examples make clear that we must intensify our work to strengthen human subjects' protection before more—and more serious—failures ensue.

An imminent organizational change within HHS will do much to facilitate our intensified efforts. Last year acting on the results of the study commissioned by the Director of the National Institutes of Health, Secretary Shalala determined that the human subjects component of the OPRR should be elevated to the Office of Public Health and Science within the Office of the Secretary. Further, the Secretary directed the Assistant Secretary for Health to carry out a national search to fill the position and to assess the resource requirements for the new office—to be called the Office of Human Research Protection. Further, she authorized the creation of a public advisory committee to help guide the new office specifically and the Department overall.

We agree with the Inspector General that the creation of the Office of Human Research Protection and its associated advisory committee presents, "a new opportunity to exert Federal leadership in protecting human research subjects." At the same time we urge research institutions to strengthen their local efforts to protect human research subjects in accord with the Inspector General's recommendations.

In particular, we urge research institutions to give their IRBs the standing and resources they need to do their job, especially during the continuing review phase. Human subjects protection is a shared responsibility among the Federal Government, research institutions, IRBs, investigators, and sponsors. HHS is committed to doing its part, and we will continue to expect others to do theirs.

My full statement describes a series of actions by HHS agencies in recent years to enhance protection of human research subjects. We view these steps as a strong beginning but concur with the Inspector General that much more remains to be done. With your permission, Mr. Chairman, I will submit my full statement for the record.

Mr. MICA. Without objection so ordered.

Dr. RAUB. On behalf of Secretary Shalala and my senior HHS colleagues, I assure the subcommittee that HHS is firmly committed to protecting human research subjects and to working actively with the research community to achieve that end. We believe that the Inspector General has provided a timely wake up call for everyone involved.

Thank you, Mr. Chairman.

[The prepared statement of Mr. Raub follows:]

STATEMENT OF

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OFFICE OF THE SECRETARY
DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOR THE HEARING ON

"HUMAN SUBJECT RESEARCH PROTECTIONS"

BEFORE

THE SUBCOMMITTEE ON CRIMINAL JUSTICE
COMMITTEE ON GOVERNMENT REFORM
U. S. HOUSE OF REPRESENTATIVES

03 MAY 2000

Good afternoon, Mr. Chairman and members of the Subcommittee. I am William Raub, Deputy Assistant Secretary for Science Policy at the Department of Health and Human Services (HHS). Thank you for this opportunity to discuss HHS efforts to protect human research subjects and to comment on the related findings and recommendations of the HHS Office of the Inspector General (OIG).

HHS Leadership in Protecting Human Research Subjects

For more than fifty years, HHS and its predecessors have led the nation and the world in the conduct, support, and oversight of clinical research aimed at improving human health. Clinical research, by definition, involves experiments. If we knew the outcome in advance, we wouldn't have to do the studies. Recognizing the risks and benefits of clinical research, HHS has extended its leadership role to protecting human research subjects from inappropriate risks.

This HHS role came about primarily because, in the years immediately following World War II, the federal government determined that the national interest would be served by investing substantial amounts of public funds in biomedical research through the then-fledgling National Institutes of Health (NIH); the investment strategy encompassed not only the direct operation of government laboratories but also awards to extramural entities such as medical schools, other institutions of higher education, and not-for-profit research institutes. In addition, the Food and Drug Administration (FDA) was assigned statutory responsibility to regulate clinical research associated with bringing drugs, vaccines and other biologics, and medical devices to market. Thus, protection of human research subjects long has been an integral part of HHS efforts to conduct, sponsor, and regulate biomedical research.

Public funding for biomedical research has been a high priority for both the Congress and the Executive Branch for the last half-century; and, during the same period, the pharmaceutical, biotechnology, and medical device industries also have been funding increasing amounts of clinical research to bring new or improved products into the health-care milieu. This ever-increasing investment by both the public and private sectors is yielding an ever-increasing fund of knowledge that, in turn, is yielding a stream of significant advances in our ability to diagnose, treat, and prevent disease.

Accompanying this series of highly productive investments has been the ever-increasing challenge to ensure that human research subjects are protected from unreasonable risks, participate of their own free will, and make their decisions only after they have been informed fully about the potential risks and possible benefits, if any, of their participation. This challenge flows directly from the Nuremburg Code -- whose principles have been adopted, reinforced, and built upon over the years in a succession of policies culminating in the current federal regulations for protection of human research subjects. HHS led the way in developing the core of these regulations -- the so-called Common Rule, which has been promulgated by 17 different Departments and Independent Agencies. Moreover, for its own programs, HHS has supplemented the Common Rule with companion requirements that address specific protections pertaining to research involving fetuses, pregnant women, and human in vitro fertilization; prisoners; and children; and FDA has promulgated its own rules, consistent to the extent practical with the Common Rule, governing clinical research associated with the products it regulates.

The primary foci for implementing these regulations and promoting compliance with them are the Institutional Review Boards (IRBs). IRBs are responsible for reviewing proposed research protocols and associated informed consent statements before subjects are recruited and clinical research begins; no project that falls under the Common Rule or FDA regulations may commence without IRB approval. Further, IRBs are responsible for continuing review -- that is, oversight of approved research projects throughout their life cycle. If, in the course of continuing review, the responsible IRB were to find cause for concern regarding the safety and well-being of research subjects, the IRB could halt the project temporarily or permanently or otherwise require the investigators to take whatever protective or corrective actions it deems appropriate.

Many IRBs are established and operated by universities, hospitals, and other institutions that receive research awards from the federal government or other sponsors. These IRBs are composed primarily of faculty and staff members who serve voluntarily and without special compensation for their IRB service; in addition, each IRB is required to have at least one member who is not a scientist and one member from outside the institution. These awardee-operated IRBs usually oversee all the clinical research conducted at their institutions -- irrespective of whether the funding for the research comes from government, foundations, or industry. In particular, most privately sponsored clinical research (e.g., drug trials sponsored by the pharmaceutical industry) is subject to review by awardee-based IRBs because much of this research is carried out in academic health centers. Research awards are the primary revenue stream available to institutions for IRB costs; many institutions receive significant funding to cover IRB operating costs by charging sponsors a fee to review privately funded research.

A small minority of IRBs operate independently -- that is, as private entities. Independent IRBs usually provide reviews for industry-sponsored projects conducted outside a university or hospital setting -- e.g., in physicians' private offices or clinics. These IRBs typically comprise paid expert consultants, operate on a fee-for-service basis, and are overseen by FDA in the same manner that FDA oversees IRBs operated by research institutions.

Two HHS components share responsibility for overseeing IRBs: the NIH Office for Protection from Research Risks (OPRR) and the FDA. OPRR oversees IRBs operated by HHS awardee institutions. FDA oversees IRBs that review clinical research related to products it regulates, irrespective of whether that research is ongoing at HHS awardee institutions or other sites.

General Comments on the OIG Findings and Recommendations

HHS is very concerned that the effectiveness of the IRBs is in jeopardy. Although the OIG investigation did not reveal either significant instances of actual harm to research subjects or evidence for any widespread pattern of outright IRB failure, we must not let that be cause for complacency. Many IRBs face unacceptably large workloads with too little time and too few resources to do everything necessary to meet the letter and spirit of the applicable regulations. The fact that instances of actual harm to research subjects have been few and far between is a credit to the extraordinary dedication and prudent decision-making of IRB members and the commitment of investigators to the integrity of their work. We must strengthen the protections now before more -- and more serious -- failures ensue.

Recent reports of several gene transfer trials with insufficient patient protections have underscored the urgency of this effort and illustrated the new pressures facing biomedical scientists, research institutions, and IRBs. For example, the line between publically funded research (primarily funded by NIH and governed by the Common Rule and other applicable regulations) and industry-funded research (aimed at bringing a product to market and governed by FDA regulations) is becoming increasingly blurred. University scientists not only may be receiving public and private funding simultaneously for related lines of research but also may be stockholders in or corporate officers of pharmaceutical, biotechnology, or medical device companies.

In the wake of the June, 1998 reports, the OPRR and the FDA stepped up the pace of their inspections of human subjects protection activities at research institutions within their respective areas of cognizance. Taken together, the findings from these inspections reinforced the OIG conclusion that the IRB system is under considerable strain. Moreover, for several institutions, the OPRR and FDA inspections led to partial or complete suspension of clinical research at those sites until the institutions' deficiencies were corrected -- often only after major revamping of the IRB structure and commitment of substantial additional resources by the research institutions. The experiences with these cited institutions suggest that HHS and the research community have considerably more work to do and that those efforts warrant a sense of urgency.

An imminent organizational change within HHS will do much to facilitate our intensified efforts to protect human research subjects. Last year, acting on the results of a study

commissioned by the Director of the NIH, Secretary Shalala determined that the human subjects component of the OPRR should be elevated to the Office of Public Health and Science within the Office of the Secretary; this action also was consistent with the results of a similar study undertaken independently by the National Bioethics Advisory Commission. Further, the Secretary allocated a Senior Executive Service slot for the directorship of the new office (the Office for Human Research Protection -- OHRP), directed the Assistant Secretary for Health to carry out a national search to fill the position while also assessing the resource requirements for the new office, and authorized the creation of a public advisory committee to help guide the OHRP specifically and the Department overall. We agree with the OIG that the creation of OHRP and its associated advisory committee presents "a new opportunity to exert Federal leadership in protecting human subjects".

At the same time, we urge research institutions to strengthen their local efforts to protect human research subjects in accord with the framework of recommendations presented by the OIG. In particular, we urge research institutions to give their IRBs the standing and resources they need to do their job properly. Human subjects protection is a shared responsibility among the federal government, research institutions, IRBs, investigators, and sponsors. HHS is committed to doing its part; and we will continue to expect others to do theirs.

We recognize that, for many research institutions, the gap between what is being done to protect research subjects and what should be done is wide and that remedial actions may be costly; but we also recognize that federal research awards already provide a substantial revenue stream that can be applied toward this end. Approximately one third of the typical research grant

is available to reimburse awardees' expenditures for the indirect costs of research -- often referred to in the vernacular as "overhead"; and approximately half of these "overhead" payments are available to reimburse expenditures in the "administration" category, which includes essentially all of the costs of operating IRBs -- among other expenses. Thus, while we recognize that many different activities legitimately claim high priority when institutions allocate their resources, we are hard-pressed to identify any activities that are of greater importance than human subjects protection.

HHS Actions Related to OIG Findings and Recommendations

Since the OIG issued its June, 1998 reports on the IRB system, HHS agencies have taken substantial steps in each of the six action categories recommended by the OIG. I am pleased to highlight some of these ongoing or planned actions for the Subcommittee's consideration. We view these steps as a strong beginning but concur with the OIG that much more remains to be done.

1. Recast Federal Requirements

In consultation with its Regulatory Burden Advisory Group, NIH developed a new policy for "just-in-time" IRB review of research proposals; the new policy will go into effect this summer. Current policy requires that the applicant institution provide NIH with results of the IRB review for each new and competing renewal clinical research grant application at or soon after the time that the institution submits the application. This means that a substantial fraction of IRB members' time and energy is expended doing reviews of proposed projects that are not likely to be funded by NIH and thus not likely to be activated. The new policy will allow the applicant

investigator to defer submission of his/her proposal to the IRB until the application has undergone the first phase of the NIH peer review process and NIH has provided the applicant investigator with the result. If, on the basis of this information, the applicant investigator determines that funding by NIH is unlikely, the institution may elect not to invoke IRB review – thereby allowing the IRB to direct more of its attention to proposed projects that have a reasonable chance of being funded as well as projects that are ongoing as a result of approval and funding at an earlier time.

Complementing the "just-in-time" initiative, OPRR has consulted with awardee institutions to streamline the assurance process -- that is, to reduce the time and documentation required for an institution to provide satisfactory evidence of its intent to comply with requirements for the protection of human research subjects. Such assurance statements generally cover a three-year period initially and then must be renewed every five years thereafter. HHS will not fund clinical research at any institution that has not provided such an assurance; moreover, failure to fulfill the terms of the assurance is grounds for enforcement action against the institution -- such as suspension of some or all its HHS-funded clinical research. The streamlined assurance process is ready to go and is slated to be introduced in the near future. This will allow both OPRR and the awardee institutions to redirect some resources to other areas, such as increased inspections and enhanced educational efforts directed toward investigators and IRB members.

2. Strengthen Continuing Protections

Another result of NIH consultations with its Regulatory Burden Advisory Group is a new requirement that Data and Safety Monitoring Boards (DSMBs) provide the responsible IRBs with summary reports of analyses of adverse events observed during clinical trials. This provides important assistance to IRBs in their continuing review of projects because DSMBs focus on their assigned trials throughout their course in more detail than an IRB realistically could do and often have expertise that is not represented on the responsible IRB. Since 1979, NIH has required that all clinical trials have some form of data and safety monitoring. In 1998, NIH reaffirmed policy by requiring that Phase III clinical trials (i.e., large-scale assessments of the safety and efficacy of a clinical intervention) have a DSMB. NIH now is developing further guidance for smaller scale clinical trials (i.e., Phase I and Phase II trials).

In a similar vein, FDA modified the Privacy Act Systems Notice to allow FDA to send sponsors and IRBs copies of correspondence to clinical investigators regarding violations of FDA regulations. Also, an FDA working group is assessing approaches to help ensure that adverse event reports associated with FDA-regulated trials are shared with the responsible IRBs in a useful manner; and another FDA working group is assessing issues related to DSMBs -- including guidelines for membership, management, quality control, value in protecting human subjects, and whether regulation is needed. All these efforts should enhance the effectiveness of IRBs' continuing review.

In March, FDA announced new protections oriented specifically to subjects participating in gene transfer trials. FDA will require that sponsors of such trials routinely submit their monitoring plans for FDA review; FDA also will perform surveillance and "for cause" inspections

of clinical trials to assess whether the plans are being followed and whether monitoring has been adequate to identify and correct critical problems. At the same time, NIH and FDA also announced their plans for a series of gene transfer safety symposia; these public forums are intended to enhance the safety of research subjects by fostering broad sharing and analysis of medical and scientific data from gene transfer research.

3. Enact Educational Requirements

Although neither NIH nor FDA has promulgated specific requirements for education, both agencies have worked assiduously to make informative materials more readily available to the research community than heretofore. For example, in March, 1999, FDA convened a national meeting that featured a presentation on the June, 1998 OIG reports. In addition, OPRR and FDA continued their series of widely acclaimed regional meetings to promote understanding of and compliance with the requirements for human subject protection; these sessions routinely are well attended by IRB members, investigators, and officials of research institutions. Further, OPRR increased its education staff, technical assistance to research institutions, and guidance documents while maintaining a web site replete with materials relevant to human subjects protection; and FDA is updating its Information Sheets, which are an important sources of guidance for IRBs and clinical investigators. We expect that the OHRP will continue and build upon the initiatives of OPRR and FDA in this regard.

In 1999, NIH established a web site called "Bioethics Resources on the Web" (http://www.nih.gov/sigs/bioethics). It provides information about bioethics initiatives at NIH and other government agencies as well as access to publications, reports, guidelines, and

regulations related to bioethics.

In 1997 and 1999, NIH issued two solicitations for grant applications related to bioethics. One initiative provides funding for short courses in research ethics. This has led to 15 awards; as a result, hundreds of investigators are taking specific bioethics courses, and many more are accessing these courses through the Internet. The other provides funding for developing scientists to enhance their knowledge and experience regarding bioethics with a view to assuming leadership roles in this area later in their careers. In addition, NIH developed and disseminated widely a template for writing easy-to-understand informed consent documents; increased its support for investigators conducting research on the informed consent process; and, in specific response to the June, 1998 OIG reports, solicited research proposals involving the development and evaluation of outcome measures to help IRBs monitor protocol review.

Within its intramural program, NIH instituted computer-based training that is mandatory for its research staff and extramural program managers who have responsibility for clinical research. The training aims to help NIH staff understand better the requirements associated with research involving human subjects. The experience here could contribute to development of an effective national web-based training effort.

4. Help Insulate IRBs from Conflicts That Threaten Their Independence

Financial conflicts of interest on the part of IRB members warrant continuing attention. The Common Rule prohibits IRB members from participating in any matter in which they have a conflict. Moreover, the potential for financial conflicts of interest to threaten objectivity is not limited to them. Similar concerns obtain for investigators and institutions as a whole, for financial

relationships related to clinical research have grown progressively more complex over the past two decades following the enactment of statutes promoting commercialization of the results of publically funded research.

The Public Health Service (PHS) and the FDA have promulgated regulations dealing with financial conflicts of interest. The PHS regulation, issued in 1994, provides for review and appropriate attention to any financial involvements of investigators that might impair their objectivity in conducting research. The FDA regulation, which became effective in 1999, requires that investigators report their financial interests to the sponsor, who, in turn, is required to report them to FDA for consideration in the course of review of marketing applications.

5. Recognize workload pressures

Initiatives to reduce workload pressures already have been mentioned in the context of recasting federal requirements; and we will continue to seek new means to relieve these pressures -- thus enhancing IRBs' abilities to provide adequate human subjects protection. However, HHS recognizes that, even with streamlined processes and the substantial recent increases in funding to research institutions via the NIH for the direct and indirect cost of research, some IRBs may not receive the resources they need to fulfill their responsibilities. HHS is prepared to work with the leaders of research institutions to address IRB functions and to understand their resource implications.

6. Reengineer federal oversight process

Several initiatives to reengineer the oversight process have been mentioned in the context of recasting federal requirements. In addition, HHS welcomes the recent interest within the research community in the concept of accreditation of IRBs. We are eager to explore this prospect and, with it, the associated issues of registration of IRBs and the credentialing of investigators. Also, we note that the National Bioethics Advisory Commission is conducting a wholesale assessment of the current system for protection of research subjects; and we look forward with having the benefits of its analysis and recommendations.

In developing the HHS' proposed rules on the privacy of individually identifiable health information, we realized that the Common Rule may not contain all of the safeguards necessary to protect the privacy of research subjects. Thus, in addition to addressing the OIG's recommendations, we also plan to begin a review of the privacy and confidentiality protections afforded by the Common Rule specifically as they relate to the subjects of records-based research.

Conclusion

HHS reaffirms its commitment to protecting human research subjects and will work actively with the research community to achieve that end. We believe that the OIG has provided a timely wake-up call for everyone involved.

Mr. MICA. Thank you for your testimony. I'm pleased now to recognize the gentleman from Maryland, Mr. Cummings, for his opening statement.

Mr. CUMMINGS. Thank you, Mr. Chairman. Conducting safe clinical trials of breakthrough medicines and treatments are critical if we are to win the war against disease and physical ailment. I can think of nothing more noble than putting your life on the line for the good of humanity. Our soldiers do it on the battlefield, and human research subjects do it in the hospitals. While both groups put their lives in danger, we must do everything we can to minimize the risks.

Today, we are here to discuss what can be done to ensure the highest level of safety possible for those who consent to enroll in clinical trials. The death last September of Jesse Gelsinger and subsequent revelations of three other deaths in a gene therapy experiment last year sponsored by Harvard Medical School has raised serious questions about current oversight procedures. Jesse's father Paul told a Senate panel earlier this year that researchers did not disclose that laboratory monkeys died following a procedure similar to the one done on his son or that several earlier human subjects sustained serious liver damage.

After the boy's death, the National Institutes of Health sent letters to researchers reminding them that they must report serious, adverse events to the NIH and the Food and Drug Administration. NIH subsequently received a flood of filings, disclosing nearly 700 previously unreported incidents of problems arising from gene therapy experiments. I think this is simply unacceptable. Seven hundred unreported incidents puts too many lives at risk. We must do better and we will. Something is failing if 700 incidents were unreported. If a real estate company withheld that many problems with their properties they would be out of business.

Today, we will hear from those who carry out the mission of oversight at the Department of Health and Human Services and the Food and Drug Administration. I'm eager to hear how they plan to address these oversight problems, and Mr. Chairman, again, I thank you for holding this hearing.

Mr. MICA. Thank you, Mr. Cummings, and Mr. Cummings also moves that the statement by Mr. Waxman, the ranking member of the full committee, be submitted for the record. Without objection, so ordered.

[The prepared statement of Hon. Henry A. Waxman follows:]

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Wednesday, May 3, 2000

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STATEMENT OF CONGRESSMAN HENRY A. WAXMAN
GOVERNMENT REFORM SUBCOMMITTEE ON HUMAN RESOURCES
HEARING ON HUMAN RESEARCH SUBJECT PROTECTIONS

Mr. Chairman, this year marks the 25th anniversary of the Federal regulations, known as the Common Rule, which established our country's basic human research subject protections. With this anniversary in mind, I applaud the Subcommittee's continuing scrutiny of the conduct of research and its oversight by Federal authorities.

Most importantly, I am pleased that today's hearing will highlight the loopholes in the law which allow some research to be conducted without government oversight. Because of these loopholes, some patients are participating in research today without the protection of the standards that apply to all Federally-funded research and research conducted at major institutions.

This is an unacceptable double standard. Today, the pace, volume and complexity of research is increasing. Universities and institutional review boards are struggling to keep pace. And recent institutional failures by the NIH, FDA and universities in overseeing gene therapy illustrate some of the continuing problems in the protection of research subjects.

These problems were also made clear by the recent suspension of research at Los Angeles County's Martin Luther King Jr. Hospital and Charles R. Drew University of Medicine and Science. This suspension follows last year's research suspension at the West Los Angeles Veterans Affairs Medical Center.in my home district.

In response to these persistent problems, Congresswoman Diana DeGette and I are developing legislation to strengthen our country's human research subject protections. Mr. Chairman, I commend you for convening this hearing and invite my colleagues to join Congresswoman DeGette and I in addressing the issues before the Subcommittee today through legislation.

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Mr. MICA. And I believe we just had those two witnesses who had statements at this time, is that correct, and the others are available for answering questions.

We'll start with some questions that I have and I'm going to address these first to Mr. Grob, Deputy Inspector General for Evaluation and Inspection. I guess sort of a basic question to start out with is, what do you consider to be the reasons for HHS' failure to implement that 1998 recommendation?

Mr. GROB. I think Mr. Raub could probably address it better than I can, but I'm willing to speculate.

Mr. MICA. You did a review here. Maybe you could tell the subcommittee what the basic problems are, one, two, three.

Mr. GROB. I think the basic problems are that the Institutional Review Boards are simply overwhelmed, and they're not able to carry out their responsibilities, particularly the oversight of research that is ongoing. I think once the research starts they don't have the ability to stay on top of it, and I think that the problems occur at that level.

Mr. MICA. We heard a description of this human research, and some of these activities started off in a fairly isolated context and numbers of universities or whoever was doing it. It's exploded. It sounds like it's difficult for the Department to get its hands around it, and then we have several agencies involved here. But we have the element of responsibility to the public. It may be jumping the gun a little bit, but maybe we should look at restructuring this whole thing or some other procedure to again keep up with the sheer volume that you described. Do you have an opinion about that?

Mr. GROB. I think it's time to think in those terms. I don't know that marginal changes around the edges will really be able to do it. I think the fundamental structure was a good idea and it worked when it started and it worked for a while, but I just think the research took off. It became far more complicated, and in a way it's almost as if the IRBs figuratively were still using manual typewriters trying to keep up with the power notebooks of the researchers. It's just something—it's a different world today, and I don't think that system has kept pace with the world. So I think it's a fair thing to say that we might need to look at different structures.

Mr. MICA. Complete reorganization of the approach. Now what about HHS, is this a priority on their scale? The other thing, too, is that Congress has also raised questions about what's going on in the oversight as we view government agency responsibility. It appears that there's been minor action and a lot of inaction. I believe, too, we had testimony that many things could be done without a lot of cost, some improvements without a great deal of costs. Maybe you could tell me first, does this appear to be a priority? Has it gotten their attention? And then, why haven't they instituted some things that were basic that could be done without a great deal of cost?

Mr. GROB. It's my feeling right now that certainly there is an intense effort being made in the Department to address these things, the problems that have been raised. I think the publicity of the troubling cases and just the general desire to do it right, the congressional hearings, the interest of the scientists in the Depart-

ment are all there. It's coming to a head. I think the interest is there now and I do expect to see some substantial changes coming down the pike.

As far as things that could be done fairly quickly, I think training and education could be done pretty well and fairly quickly. The National Institutes for Health, for example, on their own have developed training which they require their researchers to follow. They have put it up on the Web. They have got some training courses that they have made available. What's lacking is a requirement for the training and requirement for any particular standards of training, but the resources seem to be there. If they require all of their researchers, as they do, for example, to take the course that's on the Web, it seems to me that all of the grantees could take that course on the Web as well and could avail themselves of the resources. So I think that education and training of the researchers and the board members could be done pretty fast if there were a requirement to do it.

Mr. MICA. Well in 1998 you came out with a list of specific recommendations for improvement. Has HHS developed a schedule or timeframe or worked to give you any implementation schedule?

Mr. GROB. I haven't seen a time schedule like that, that went recommendation by recommendation with a time schedule.

Mr. MICA. Let me just ask a quick question now. Of course, every agency comes to Members of Congress now and says just give us more resources and we can handle the job. But we had recommendations that had been made that folks testified to that could be implemented with fairly low cost and things that could be done to improve oversight, operation and function. I have two questions then for Dr. Raub. One, what's the status of those low cost things that could be done within budget? And then second, I guess you have already submitted your 2001 budget. What kinds of requests for additional resources or personnel were included in the Secretary's request?

Dr. RAUB. Thank you, Mr. Chairman. With respect to the overall question, we've taken the recommendations of the Inspector General to heart and have in fact undertaken some substantial efforts over the last several years and will continue to do so. As I indicated in my prepared statement, we think they're, while substantial, that nowhere near enough; and we will continue to intensify that effort.

Among the things we have done within the available resources are the following. I indicated the stepped up investigations and inspections, both by the OPRR and the FDA.

Mr. MICA. Is that what was referred to from 1 to 10?

Mr. GROB. It's a lot more than that. My opening statement was of course in the 5-minutes, but there have been increases in the number of non-onsite reviews that the NIH has made, and the FDA has made about a 50 percent increase in the number of site visits that it makes.

Mr. MICA. Is that adequate?

Mr. GROB. No. We need more.

Mr. MICA. So those are some things you started. I'm sorry, Dr. Raub, continue.

Dr. RAUB. And along that line, just continuing Mr. Grob's thought there, while the returns on those investigations have been disappointing in the sense of identifying some widespread pattern of problems and have led to enforcement actions, those enforcement actions have a secondary effect in the sense of promoting compliance elsewhere—indicated by the Inspector General as a sentinel effect. So we believe that the expenditure of those funds dealing with individual problems has in fact had a positive effect in terms of making the larger community sensitive to the need for more attention and more investment of resources in these activities.

Mr. MICA. Now, enforcement. When we had the hearing last time, there was one instance of a suspension reported, one or two. Since that time, what's the status? Usually enforcement would indicate that there's some penalty or there's some suspension of funds taking place. What's taken place in that regard?

Dr. RAUB. I'll comment generally, and, if I might, ask Dr. Ellis and Mr. Michels if they want to add some details to it; but in essence the thrust of the suspensions is not only to stop the activity and put an immediate protection in place but, more important, to require certain remedial actions on the part of the institutions to ensure that the problems are solved and the protections are in place. And that's been a pattern on these various ones.

Mr. MICA. My question dealt with has there been any suspension of funds since the last hearing or penalty actions? Remedial actions are fine, but I want to know, if somebody gets some penalty, then does it have an effect down the line on others to sort of straighten up their act?

Dr. RAUB. Let me ask my colleagues to address that.

Mr. MICA. Identify yourself for the record, please.

Mr. ELLIS. My name is Gary Ellis, Director of the Office of Protection from Research Risks, and chairman of the Interagency Human Subjects Committee. For research that is funded by the Department of Health and Human Services the ultimate penalty is a cessation of funding.

Mr. MICA. Has there been any since the last time? Now what we've discovered there are more problems than we anticipate and the Inspector General talked about finding a pattern of problems far in excess of what I think we even expected. Then we heard that we were taking some enforcement actions that were part of the corrective pattern. My question is, what type of enforcement actions?

Mr. ELLIS. Well, since the June 1998 hearing and the Inspector General's report, OPRR has evaluated the protection of human subjects at a couple dozen institutions. There have probably been about 10 site visits during that period, and in virtually every case we've made findings of shortcomings with regard to human subject regulations and required remedial action. In a few noteworthy cases at the Duke University Medical Center in May 1999 and just a small number of other institutions, we have actually ordered an interruption in research. Virginia Commonwealth University in January 2000 as with Duke, we ordered an interruption in research. These are extreme cases and an extreme action was taken, the interruption of research.

Mr. MICA. In two cases?

Mr. ELLIS. There were other cases where we imposed restrictions but we didn't have the suspension that you note. The Food and Drug Administration took an action——

Mr. MICA. Was it the suspension of the program or suspension of funding or both?

Mr. ELLIS. Suspension of the program. The Food and Drug Administration took action at the University of Colorado Health Sciences Center, and Dan might want to talk about that.

Mr. MICA. Identify yourself for the record.

Mr. MICHELS. Yes, sir. I am Daniel Michels, Director of the Office of Enforcement at FDA.

I think you've put your finger on an important issue from the standpoint that the action available to both our organizations is an extreme one; that is, the authority to shut down an operation in its entirety. The threat of that most frequently causes either a voluntary shutdown before we need to deal with that or else a great deal of willingness to do the right thing and get back on the right track. One of the things that we are exploring is the possibility of asking the Congress for intermediate remedies that might be less than throwing the atom bomb, if you will, to deal with these situations.

Mr. MICA. You don't feel that you have the authority to do that?

Mr. MICHELS. That is correct in this particular instance, and I want to reinforce and I think Representative Kucinich made the point very eloquently, is too often the IRBs are underfunded. The willingness to do the right thing is there, but they do not have the resources and support to do it, and our taking enforcement action will result hopefully in that kind of funding somewhere downstream, but we would much rather see education happen first, do the right job the first time in a well-funded situation.

Mr. MICA. Mr. Cummings, I have additional questions. Did you want me to yield to you at this time and come back, do a second round? Is that OK? Or do you want me to proceed?

Mr. CUMMINGS. No. I just have a few.

Mr. MICA. All right. I'll recognize Mr. Cummings, and I do have an additional round of questions.

Mr. CUMMINGS. I was just wondering, what kind of—following up on what the chairman asked about—what kind of sanctions would you like to see, I mean, would you like to have the authority to use?

Mr. MICHELS. Unfortunately, the thinking is a little bit early on this. One of the things that we've thought about is civil money penalties, but again, fining an organization which is poor already doesn't seem to be a very good option. If we could find something more prescriptive, that is more targeted to the particular problems that an institution has rather than simply shutting down the whole engine, we would be possibly better off than we are now, but that's the best I can do for you at the moment, Congressman.

Mr. CUMMINGS. Why would an organization when threatened with a shutdown voluntarily shut down as oppose to say straightening up the matter? I mean I know you said sometimes they do, but sometimes they just go on and shut down. I mean what kind of situations would cause that?

Mr. MICHELS. Well, the recognition that something major needs to happen and rather than having the terms dictated, if you will, by the regulatory agency, they see the light and say OK, before that letter of shutdown is received, here's our plan, this is what we're going to do. In the meantime we are going to suspend some or all of our operation as a signal of good faith. As a regulator, I wouldn't be necessarily too thrilled to see somebody make some offers without doing something immediate and protecting those folks that are at risk.

Mr. CUMMINGS. Mr. Ellis, in 1998 I think you told the subcommittee that your office was pursuing about 70 open investigations.

Mr. ELLIS. That's correct, sir.

Mr. CUMMINGS. How many of those cases have been closed?

Mr. ELLIS. That's something I'll have to get back to you on. A large number remain open. Today we actually have 163 open investigations.

Mr. CUMMINGS. So in 2 years the number of open investigations have more than doubled.

Mr. ELLIS. That's correct. Some of the 70 to which you refer have closed, but many more have opened since that date.

Mr. CUMMINGS. Why do you think that is? I mean, that's a lot of cases. I mean, when you look at 70, some have been closed and now you're up to 163. Why is that?

Mr. ELLIS. We are receiving more complaints. The issue of protecting human subjects in research has been featured in the press. Our complaints come from citizens, they come from research institutions themselves, from employees at research institutions that see things they don't like. In some cases from human subjects who feel they have been harmed or wronged in some way. Our office was not all that prominent, perhaps hard to find, and now it's easier to find for complainants. That's my best explanation.

Mr. CUMMINGS. How many employees do you have doing the investigations on human and animal subject research?

Mr. ELLIS. Our office was originally split so the animal welfare staff are now in a different office, but with regard to human subject investigations we have two full time equivalent investigators. Actually a full time physician, a half time physician and a half time attorney handle 163 cases.

Mr. CUMMINGS. And how many do you think you need to do an adequate job?

Mr. ELLIS. One could work through the arithmetic of what a serious caseload would be for a high level professional. The Public Health Service Act requires a prompt, that's a quote, a prompt resolution of the cases. We could work out the arithmetic if we took prompt to mean 6 months, let's say, how many cases an individual can move and get 6-month closure. It's something I could calculate for you.

Mr. CUMMINGS. That's OK. Is there a statutory requirement to report adverse events to your office?

Mr. ELLIS. There's a regulatory requirement that pertains to research funded or conducted by any of the 17 departments and agencies that have been in place for years, the institutions must report unanticipated problems involving risks to subjects or others.

That is one kind of report. The second kind of report is any suspension or termination of Institutional Review Board approval. And the third kind of report is any serious deviation or noncompliance with the regulation. The answer is yes.

Mr. CUMMINGS. Those reports that you just talked about, how many have you received over the last year?

Mr. ELLIS. In 1999 we received 187 reports of that type from I think about 87 institutions.

Mr. CUMMINGS. Mr. Raub, back in December Dr. Art Lawrence testified before us in a hearing we held in New York, and at that time Dr. Lawrence assured us that the Office of Protection from Research Risks would be moved to the Office of the Secretary and a new director would be selected by March 2000. It's now May and can you tell us where we are on that?

Dr. RAUB. Yes, sir. The Department is close to completing those actions, but it has taken somewhat longer than the original estimates. I'm hopeful, as is Assistant Secretary Satcher, that the appointment of a director for the new Office of Human Research Protections is imminent. We hope in the next few weeks at the least for the announcement of that appointment, and with that then the formalization of the move of the office from NIH to the Office of the Secretary and the establishment of the new advisory committee.

Mr. CUMMINGS. Well, while in New York Dr. Lawrence also testified, and he even introduced a letter from Dr. Satcher which said that the advisory panel would be created which would be responsible for human subject research protection. Is that the advisory panel you were just talking about?

Dr. RAUB. Yes, it is.

Mr. CUMMINGS. And how do you see that as helping this problem, I mean the appointment of that panel?

Dr. RAUB. Well, first of all, we see the relocation of the office as giving it the higher visibility in terms of the Office of the Secretary and an underscoring of the Secretary's commitment to this. Second, as part of the move, the Secretary directed Assistant Secretary Satcher to commission a study of resources along the lines of the question that you were just addressing to Mr. Ellis; and that study, as I understand it, is either complete or near so. It will be an important factor in the future budgeting decisions for this office.

The advisory committee is intended to ensure that we have a public, high level and highly qualified group of individuals drawn broadly from the research community and the interested general public who can provide a continuing forum of advice and criticism for the Department as we move to set priorities and do what we can to ensure that these human subjects protections are in place. We have not had that kind of forum before in the Department, and we think it's much needed, and I'm optimistic as to what it will be able to provide for us.

Mr. CUMMINGS. Right now, do you have to go—is part of the processes that you use the Federal Register?

Dr. RAUB. For what, sir?

Mr. CUMMINGS. For the advisory panel.

Dr. RAUB. The advisory panel will be created under the terms of the Federal Advisory Committee Act, and those actions have been taken in terms of securing the necessary slot and authorization to

do it. Most likely what we will do is announce in the Federal Register the functions and other expectations for the committee, and as we do with many other advisory groups, invite nominations of members from interested members of the public, and then put together a recommended slate or alternative slates for consideration by Dr. Satcher and the Secretary.

Mr. CUMMINGS. Thank you.

Mr. MICA. Thank you, Mr. Cummings. I didn't get the answer when I yielded to Mr. Cummings about the second part of my question. What was the number of personnel requested in 2000 to 2001. Again, we've identified that there's a problem. Some of the answer is more personnel, more resources. Can you tell me requests for additional slots?

Dr. RAUB. Sir, I don't have those figures with me.

Mr. MICA. Does anybody have them?

Dr. RAUB. I'll be pleased to provide them for the record.

Mr. MICA. Mr. Ellis, do you? You said you could calculate, but this isn't something that just snuck up on us today. It's a problem we've known about, and one of the ways that we resolve it is by applying the necessary resources, putting the requests through the process, and nobody knows what we have requested? Maybe somebody could slip somebody a paper with a magic number on it. No? And you don't have a recommendation to the subcommittee about what kind of resources it would take?

Dr. RAUB. Again, I don't have the budget figures with me. I'd be glad to provide them for the record, sir.

Mr. MICA. Mr. Grob, the situation seems to be mushrooming out of control, both the sheer number of Federal dollars involved in this human experimentation and then this large universe outside of commercial activity. I think you spoke to some of that. What are we looking at as far as percentages in each of these areas of experimentation, federally funded and nonfederally funded? Would you care to venture a guess, Mr. Grob?

Mr. GROB. I don't know about the exact number. Certainly we're talking about billions of dollars in both cases. An easy way to think of it is most of the commercially funded research that we're talking about here would be research that's connected with the proposed drugs and medical devices that are overseen by the Food and Drug Administration. So their entire workload of oversight would be commercially funded, whereas the National Institutes of Health would be those that are funded by our Department. Now of course there's these other Federal departments that also fund on the Federal level their research. So I'd say it's billions and billions, but which—you know, what the exact amounts are I can't tell you.

Mr. YESSIAN. My name is Mark Yessian. I am the regional Inspector General. At some of the major medical centers that we visited and talked to, about half the applications that the IRBs are getting are coming from commercial sponsors these days so that helps put it in a little perspective.

Mr. MICA. Another question that was raised at the last hearing, which continues to be a concern, is the problem with commercial activities and other interests in this whole operation, the conflict of interest. I think there was a recent Los Angeles Times article that alleged the U.S. Government's top diabetes researcher helped

guide a $150 million Federal study involving Rezulin while serving as a paid consultant for the drug manufacturer, which was Warner Lambert Co. What's the Federal Government's policy regarding outside employment and conflicts of interest, Mr. Raub?

Dr. RAUB. Sir, there are several elements to that. First off, the changes in the nature and the patterns of financial relationships are one of those changing elements that Mr. Grob and his colleagues had mentioned. It's quite a different situation than, say, 20 years ago. A major impetus for that has been some statutory changes designed to promote the commercialization of publicly funded research. And, for the many highly desirable results of that, it has created a pattern of relationships where not only do some of the universities' and academic health centers, for example, receive a substantial amount of funding from the private sector—some on the order of half, as Mr. Yessian indicates—we also have instances where some of the university professors also have either stock holdings or even serve as corporate officials for some of the private organizations, some of which may be sponsoring the research.

A major element already in place related to that is a public health service regulation that requires all of the entities funded by the agencies of the Public Health Service, that is the universities and other recipients of awards, to have in place a policy and a system to identify actual or apparent conflicts of interests that might affect the scientists' participation and to take such steps as are necessary to manage those conflicts—in some instances removing the conflict, in others putting certain safeguards in place.

One of the areas where we will be intensifying our effort is trying to find ways to ensure that, as those procedures relate to human subject protections, some of the kinds of safeguards we have in place will be those against the potential coercion of subjects in research as well as guarding against things that would create less than full objectivity in the way experiments are designed, patients are recruited, or results are presented. This will be a continuing challenge for the entire research community.

Mr. MICA. Is it necessary for additional legislation, corrective legislation to deal with the new set of emerging conflicts and circumstances?

Dr. RAUB. In my judgment, sir, no. The Public Health Service regulation to which I referred and, a companion regulation that the Food and Drug Administration has dealing with reporting of financial conflicts of interests, gives a considerable set of tools to use here. I believe the task will be building on those tools and using them most effectively. I am sure the Department won't hesitate to propose legislation if it concludes that's necessary, but we don't think so now.

Mr. MICA. I don't want to pick anybody out, but in this case I just cited, this individual who served as a paid consultant to the drug manufacturer was I believe a Dr. Eastman, who had this employment as a consultant, and it appears to be a conflict of interest. Do you know if you all investigated this particular arrangement to see if there was a conflict of interest?

Dr. RAUB. I don't know the full details, sir. I know that an investigation was carried out at the NIH. I don't know that it's completed. We can provide a report for that to the subcommittee.

Mr. MICA. Well, I'd like to know because if you feel that we don't need additional laws then you have at least the authority to proceed, and we want to make certain that there is some attention to the problem of conflict of interest that has been raised to us. I have other cases here and I won't be able to get into all of them. We could submit some of them for questions to you, but it appears that some of the problems we've had—now conflict of interest is one thing. Maybe we picked that up through the media. I think you all have testified that you're picking up problems that have resulted sometimes in death in these experimentation cases where there hasn't been, I think we're going to have witnesses about the full disclosure, prior disclosure about oversight, about the proper functioning of the review process, which is a big concern to us. We have an agency, and maybe it is short on some resources, but in fact we are told that it's somewhat dysfunctional and even no cost or low cost recommendations have not been instituted. So I have to cite these as major concerns of the committee.

And then we have another area now, this growing area of a commercial activity that doesn't fit. We don't have the handle because we don't have the Federal funds into the activity, and FDA has some responsibility, but there are some instances here in which there appear to be a gap, which is another problem. Did you want to comment on that briefly, Mr. Grob?

Mr. GROB. We don't know the extent of that, but that's probably small but growing, where there is research that's going on that's not connected with any proposal for a Federal approval of a drug or device and they're not the result of a Federal grant. In those cases there are no requirements for Institutional Review Boards or for some of these other protections. Just simply good practice would call for it, but the extent to which it's happening and the type of controls over that is just sort of an area that's not well-known or understood at this time.

Mr. MICA. And what's interesting, too, is there are so many new research techniques in biogenetics, I mean, I just can go on and on about things that are happening almost on a daily basis that the law is not keeping up with. I am wondering if we really need to take a closer look at this, some of these gaps and again have in place some mechanism to deal with this in the future. Mr. Michels.

Mr. MICHELS. Yes, sir. Thank you, Mr. Chairman. I just wanted to clarify that the Food and Drug Administration is working in the area of, if you will, noncommercial research from the standpoint that there are requirements from time to time that, notwithstanding the intent to market the product, if it is being used as an experimental agent on people it should be covered by an investigational application.

I think what is maybe troublesome to some folks is the zone in between where an investigator, a clinical investigator may also be the entrepreneur who is intending to ultimately develop the product him or herself rather than working as an employee or agent for a major pharmaceutical house, for example. The roles have become very blurred here, and we also are puzzling over where we need to

be drawing the lines. I would suggest again we go back to the principle that was laid out very early in your hearing today, and that is we need to be educating all of the scientists, be they clinical investigators, the researchers, the IRBs, as to what the requirements are, minimize their impact so that the right decisions are made on behalf of the subjects being exposed.

Mr. MICA. Thank you. I'm not going to give you an opportunity to respond because we have a vote. I have less than 4 minutes to get to the floor. I am going to excuse the panel. We're going to submit some questions. I have some specific questions on cases, Mr. Ellis, but I'll tell you, Mr. Raub, that we've got to do something to get into place some of these recommendations.

Mr. Cummings described some of the foot dragging and some of the things in simple appointments, getting people in place, making low cost or no cost recommendations, getting us to recommendations. We have got to do something. If necessary I'll hold another hearing and call everybody back, and we'll subpoena the Secretary if we have to to get something moving in this area. But I just give you that.

Without objection, we will submit to you further questions and ask for your written response. We'll stand in recess for approximately 15 minutes, until the conclusion of the next vote.

[Recess.]

Mr. MICA. I'd like to call the subcommittee back to order. I want to go ahead and proceed. We have our second panel before us at this point. Unfortunately, there may be a vote in the full committee. There's been a full committee hearing going on while we're conducting this subcommittee hearing. We may need to recess at some point if a vote is called in that body.

Our second panel consists of Mr. Richard Curtin, and he I believe was a human subject in one of these research experiments. We also have Charles R. McCarthy, and he is a senior research fellow at the Kennedy Institute of Ethics at Georgetown University, and then we also have Dr. Robert Amdur, and Dr. Amdur is the associate professor and associate chair of clinical affairs at the Department of Radiology and Oncology at the University of Florida. Good to see someone from my alma mater here. If we could just get a President now we'd be in good shape. That's an inside matter.

I'd like to welcome all three of our panelists this afternoon. Let me go ahead and explain the ground rules. I think you're all new witnesses. We do swear in our witnesses. This is an investigations and oversight subcommittee of Congress. I'll swear you in in just a minute. I'm going to ask you to limit your oral testimony to 5 minutes. Upon request, we'll put in any full statements or additional information in the record deemed appropriate, upon request through the Chair. With that, I will swear you in, if you'd stand, please.

[Witnesses sworn.]

Mr. MICA. Witnesses answered in the affirmative. I welcome the witnesses. I think we'll call on Richard Curtin, who was involved in one of these research projects. He's from Falls Church, VA. Welcome, sir, and you're recognized.

STATEMENTS OF RICHARD CURTIN, HUMAN SUBJECT, FALLS CHURCH, VA; CHARLES R. McCARTHY, SENIOR RESEARCH FELLOW, KENNEDY INSTITUTE OF ETHICS, GEORGETOWN UNIVERSITY; AND ROBERT AMDUR, M.D., ASSOCIATE PROFESSOR, ASSOCIATE CHAIR, CLINICAL AFFAIRS, DEPARTMENT OF RADIOLOGY AND ONCOLOGY, UNIVERSITY OF FLORIDA

Mr. CURTIN. I'd like to thank the subcommittee for inviting me to appear today, but I have to admit I'm surprised to find myself in the position of being so critical——

Mr. MICA. You might pull that mic a little bit closer if you could. Maybe you can do that with your book there.

Mr. CURTIN. I'm surprised to find myself being in a position where I'm being so critical of genetic research. I have a Master's Degree in human genetics, and 25 years ago I was working with the Director of NIH in an effort to convince the Congress to go ahead with funding for cutting edge recombinant DNA research. But in September 1998 I was introduced to a different aspect of genetics research when my daughter Allison received the Virginia Twin Study sponsored by Virginia Commonwealth University.

The study consisted of a 25-page questionnaire asking hundreds of questions about a person's medical history. When I looked through the questionnaire I was surprised to find that 176 of these questions involved not only my daughter's medical history but also the medical histories of her mother, her brother and me. In other words, she was being asked to comment upon the medical history for the entire family.

I was further shocked by the bizarre nature of some of these questions. For example, the study asked if any of us had suffered from depression, infertility, alcoholism, or schizophrenia. It asked if Allison's brother or I had abnormal genitalia, sperm abnormalities or low sperm count, and it asked if Allison's mother had any diseases of the genital tract or if her menstrual periods were unusually long or strong. Nowhere in the study packet were the words "informed consent" ever mentioned, and this package was addressed strictly to my daughter.

I was outraged that a federally funded project would attempt to violate my family's privacy in this manner. I immediately wrote to the principal investigator of the study and also to the chairman of the Institutional Review Board. All I asked them to do was to remove the columns for the other family members and to send separate questionnaires to each of us. I realized that this would have cost them more and it might have cut down on the response rate, but the data base would have been more accurate, and it also would have avoided the problem with informed consent.

The chairman of the Institutional Review Board just didn't bother to respond at all. The principal investigator, responded but her response was so demeaning and so arrogant that it probably would have been better if she hadn't responded either. It became very clear to me that the concerns I raised were not going to be addressed to my satisfaction by the people at Virginia Commonwealth University.

So I filed a complain with OPRR. OPRR concluded that the internal controls for the protection of research subjects at the university

were so inadequate that all federally funded research had to be shut down until proper controls could be put into place. The sum total of this action was 1,100 research projects suspended.

With the chairman's permission, I'd like to enter into the record a summary list that I've prepared listing 19 deficiencies that OPRR listed from its investigation at Virginia Commonwealth University.

Mr. MICA. Without objection, that will be made part of the record. Proceed.

Mr. CURTIN. Thank you. Rather than addressing the legitimacy of the deficiencies found at Virginia Commonwealth, the leadership of the genetics research community decided to take a different approach. They went on the attack. They went after OPRR. I'm especially offended by the positions taken by two of their main leaders, Dr. Edward McCabe, chairman of the Secretary's Advisory Committee on Genetic Testing, and Dr. Francis Collins, Director of the National Human Genome Research Institute at NIH. These gentlemen have argued in writing that, even within a family, once a piece of medical information becomes known to one other person within that family there is no longer any expectation of privacy and there is no need for any researcher to bother getting the informed consent of the family members.

A little anecdote, also about this time, my daughter was home for Christmas vacation and asked if I would call the University of Virginia registrar to find out one of her grades. So I made the phone call and explained to the registrar's office that I was her father, but they would not release her grade to me because it was a violation of her privacy. Despite the fact that she was my dependent and I was paying the tuition, they wouldn't tell me her grade. But the people at the Virginia Twin Study fully expected her to go around and tell the most intimate nature of the medical histories of not only herself, which I wouldn't mind her doing, but also of every other member of her family.

I've been involved with this issue now for 20 months and I've reached five basic conclusions. One, the public cannot rely upon individual researchers to adhere to the rules and regulations that go along with the acceptance of Federal funding. When a research protocol does not go as planned, the initial reaction of the researcher seems to be to cover it up.

No. 2, the public cannot rely upon Institutional Review Boards to ensure that guidelines are followed and that experiments are scientifically and ethically sound. Basically, I don't believe that colleagues at the same institution can be trusted to critically review and police each other's work. If I criticize your work today, what's going to happen when I come in front of the IRB tomorrow?

Three, the staffing and funding levels at the Office of Protection from Research Risks have been designed to ensure that OPRR will not be too effective. Other speakers have mentioned this, and it's very, very clear to me that OPRR has been treated as a proverbial stepchild within the NIH family.

Four, the research community, in my opinion, is in a state of denial regarding the trouble that it's in. They have allowed a regulatory vacuum to exist and a trust gap to develop, and now others are rushing in to fill this vacuum and to close this gap. The com-

munity strategy of stonewalling, covering up and attacking will not, I don't believe, be successful in the long run.

Five, potential solutions. It's obvious that OPRR needs to be upgraded, but you also have to be realistic about how much a centralized office here in Washington can do when the research is so decentralized. In my opinion, therefore, the quickest, least expensive and possibly most effective course of action is for each researcher to realize that violations of guidelines and regulations will have very serious consequences. If the probability of getting caught is going to be low, then the consequence of getting caught should be very severe.

One of the members asked earlier what other penalties could we possibly have. I have a suggestion. I suggest that a principal investigator who fails to file a timely and accurate adverse event report might be suspended from the project for 1 year. Allow the project to continue so that the benefits of the research aren't lost, but let it continue under someone else's leadership.

Mr. MICA. Excuse me, but I'm going to have to recess the hearing for just approximately 10 minutes. We do have a vote in the other committee. We'll continue when I return.

[Recess.]

Mr. MICA. I will call the subcommittee back to order. I apologize for the delay, but all members of the full committee were summoned. To get back here, let's see, we had Mr. Curtin who was interrupted as he had some closing remarks I believe. So if you would sum up your testimony, Mr. Curtin, you're recognized.

Mr. CURTIN. Yes, sir. Just finishing up, two possible penalties to suggest. One is, as I was mentioning before, suspension of the principal investigator while his project still goes on. A second possible penalty would be making that investigator unable to compete for future grants or contracts for a certain period of time. Those are two suggestions. I don't think it's that hard to find penalties that fit the problem.

I want to thank you for the opportunity to express my concerns and my opinions, and I would like to submit a more lengthy statement for the record with the chairman's permission.

[The prepared statement of Mr. Curtin follows:]

PREPARED STATEMENT OF RICHARD CURTIN

PRESENTED TO THE

SUBCOMMITTEE ON CRIMINAL JUSTICE, DRUG POLICY, AND HUMAN RESOURCES

MAY 3, 2000

The staff of this committee learned of my existence because I was the subject of a recent article in the Washington Post. This article described how a complaint that I filed with the Office for Protection from Research Risks led to the shutting down of all federally funded biomedical research at Virginia Commonwealth University (which includes the Medical College of Virginia).

The irony of this situation is that approximately 25 years ago I was working with the Director of the National Institutes of Health to convince the Congress and the public that recombinant DNA research was safe and should be allowed to go forward (after specific safety procedures had been put into place). In other words, I am a very unlikely candidate to be appearing before a congressional committee arguing for more effective constraints on the conduct of genetics research.

Let me explain how this reversal in roles occurred.

MY INTRODUCTION TO THE VIRGINIA TWIN STUDY

I am the father of twin children born in Virginia in 1978. In September 1998 my daughter, Allison, received a large envelope from Virginia Commonwealth University (VCU) containing a questionnaire entitled "The Virginia Twin Study." I have a background in the development of survey questionnaires, and several things about this questionnaire seemed unusual:

- First, the questionnaire was ***25 pages*** long. The typical respondent does not have the motivation to accurately complete an unsolicited survey of this size. Regardless of how important their participation may seem, most people will not react well to such a long and complex questionnaire.

- Second, ***176*** of the questions asked the respondent to provide ***detailed medical information about every other member of the immediate family***. There was no suggestion that the respondent might want to discuss the survey with the family members before answering the questions.

- Third, ***the nature of many questions*** was so unusual that I eventually organized them into four categories based upon (a) whether my daughter was qualified to respond and (b) whether or not she should respond:

CATEGORY I - OBVIOUS, SHARED INFORMATION

Conditions such as cleft lip, extra fingers, and Down Syndrome are obvious and are understandable to a person without any medical training. For these conditions, the twin could be expected to answer accurately without violating the privacy of a family member.

CATEGORY II - BORDERLINE OFFENSIVE QUESTIONS

A question such as "does any family member have extra nipples" is a little troublesome to me. Even if the twin knows the answer, should she provide the information? Would this violate the privacy of a family member? This, in my opinion, is a close call.

CATEGORY III - QUESTIONS REQUIRING SOME MEDICAL KNOWLEDGE

My daughter would have no idea whether arthritis is osteo or rheumatoid; whether an ulcer is of the stomach or the duodenum; whether the thyroidism is hyper or hypo; or, whether the seizure is grand mal, petit mal, prolonged, psychomotor, temporal lobe, complex partial, or epilepsy.

CATEGORY IV - YOU HAVE GOT TO BE KIDDING!!!!

Where does any researcher get the nerve to ask one family member to report whether another family member suffers from abnormal genitalia, depression, infertility, alcoholism, schizophrenia, length & strength of menstrual periods, other diseases in the female genital tract, low sperm count, or sperm abnormalities. These conditions should have ***an expectation of privacy*** and ***a requirement for informed consent*** before they are revealed.

MY ATTEMPTS TO WORK WITH THE RESEARCHERS AT VCU

I wrote to the principal investigator of the Twin Study and to the chairman of the institutional review board at Virginia Commonwealth University asking them, in the future, to send separate questionnaires to each family member. If you want to know about my genitalia, ask me directly. Don't ask a third party. Sending multiple questionnaires would increase the cost of collecting the data and may reduce the response rate, but it would also have two very significant benefits: the database would be more accurate and all respondents would have given their informed consent.

The researcher's response back to me was insulting:

- She maintained that "participation...is entirely voluntary." This is a ridiculous position. The twin who receives the questionnaire can decide whether or not to participate in the study, but the other family members are not provided this opportunity by the principal investigator.

- She assured me that the information in the database was "strictly confidential." But, in a later correspondence, she admitted that the security of the database needed improvement and the information was subject to disclosure under a federal subpoena.

But at least the principal investigator responded to my letter. The chairman of the institutional review board completely ignored me!

So I wrote to my congressman and state senator, and they forwarded letters they received from the principal investigator and the chairman of the Department of Human Genetics at Virginia Commonwealth University. Their responses just made me angrier:

- The review of protocols for safeguarding the rights of human subjects followed current NIH guidelines. ***But OPRR determined that the Twin Study was, in fact, out of compliance with regulations.***

- The questionnaire was approved by the institutional review board. ***But OPRR determined that the performance of this board was so defective that it had to be completely disbanded and replaced with a new board comprised of members from outside of Virginia Commonwealth University.***

O There is no way of understanding the etiology of these conditions without the collection of family history data. ***In other words, interfering with the Twin Study would be a huge setback to the health of mankind.***

O The question of who owns a family history is a frequently discussed dilemma in human genetics. ***But I don't see the dilemma. It's my medical history, so I own it. I never granted co-ownership to my daughter.***

O Virginia Commonwealth University has been doing this for over 20 years; no one has ever been injured by answering these questions; this is the first time anyone has ever complained; many people have benefited from the study; and, others should not be denied the right to choose whether or not to participate. ***In other words, there is nothing wrong with the study. There is something wrong with me for objecting to the study.***

But my favorite response was, "We have often used these data to seek grant support for more definitive studies." ***In other words, the Twin Study is a cash cow for the university!***

It became very clear that the concerns I raised were not going to be addressed to my satisfaction by the staff at Virginia Commonwealth. So I wrote to the Office of Protection from Research Risks (OPRR). It took OPRR a year to address my complaint, but, when they did, they concluded that the internal controls for the protection of research subjects at Virginia Commonwealth University were so bad that all research had to cease.

THE SCIENTIFIC COMMUNITY ATTACKS OPRR

After OPRR issued its findings, I thought my involvement in this issue was concluded. But then I became aware of the response of the leadership of the genetics research community, and all the anger that I experienced in September 1998 came rushing back to the surface.

I ***expected*** the leadership to tell its community that the Virginia Twin Study protocol needed adjustment; the performance of the institutional review board at Virginia Commonwealth University was unsatisfactory; and, they were going to work closely with OPRR to improve compliance with the laws, rules, and regulations governing genetics research.

Instead, the leadership attacked OPRR's decisions and actions. I was especially offended by the positions taken by Dr. Edward McCabe, Chairman of the Secretary of HHS Advisory Committee on Genetic Testing, and Dr. Francis Collins, Director of the National Human Genome Research Institute at NIH. The former was quoted as stating, ***"where it is communal information within a family, meaning it is held by more than one person, then I think it is not private."*** The latter wrote, ***"In my view, family information is shared information...(and) the sharing of such information cannot and should not be limited only to those parents and siblings who consent for the information to be shared."*** These gentlemen apparently believe that the exchange of information within a family deserves no more expectation of privacy than things that are mentioned or seen at the health club or the local tavern.

Their comments brought to mind a phone call I once made to the University of Virginia asking about my daughter's grades. Despite the fact that she is my dependent and I was paying the tuition, the university would not give me her grades because this was considered a violation of her privacy! But Drs. McCabe and Collins would have you believe that ***it is not a violation of my privacy to ask a third party*** about my mental health, my genitalia, the condition of my sperm, etc.

I also was upset by ***the level of hyperbole emanating from, and the knee jerk reaction of, the research community***. To listen to these scientists, you would think that genetics research was going to come to a screeching halt because some madman in Northern Virginia filed a complaint with the federal government and the idiots in the government then sustained his complaint!

And let's get one argument off the table right now: I do not object to my daughter discussing family medical history with her ***doctor***. There is no comparison between a questionnaire from a faceless researcher and a question asked by a physician during an examination. If Allison's doctor asked about the appearance of my genitalia, I would assume that there was a specific connection between this question and the ability of the physician to make an accurate assessment of her health. Under this circumstance, I would want her to discuss my abnormal genitalia without first seeking my consent. (But I assure you, that physician later would receive a call from me asking for an explanation of the relevance of the question.)

And finally, I was surprised by ***the inability of this community to recognize the severity of the problems*** it is facing. They have allowed a regulatory vacuum and a trust gap to develop. And now, others are rushing in to fill this vacuum and to close this gap. Investigative journalists have been looking into their activities. A privacy office has been established within the Office of Management and Budget. The Inspector General at the Department of Health & Human Services (HHS) has issued a critical report. The General Accounting Office has issued a critical report. And Congress is now holding hearings and considering the passage of restrictive legislation. The research community is taking a very big risk if it assumes that this controversy will pass away with time. Their strategies of stonewalling, covering up, and going on the attack will not work.

EXACTLY WHAT IS IT THAT I WANT?

Remember, ***I never asked for the Virginia Twin Study to be shut down***. Back in the fall of 1998, all I ever wanted was for the investigator to obtain the informed consent of all family members.

But that was before I knew exactly how bad the situation was. Knowing what I now know, I am convinced that the public cannot rely upon individual scientists, or upon a group of scientists formed into an institutional review board, to regulate this research. ***Knowing the right thing to do is easy. But doing it takes some courage***. And the genetics research community has not demonstrated that is possesses this kind of courage.

A very disturbing example of the failure of individual scientists to do the right thing was reported recently by the Washington Post. Two people died during a gene therapy experiment in a Boston hospital, but NIH learned of these deaths only after a third person died. NIH then sent out a notice reminding gene researchers of their obligation to report adverse events. NIH then received a flood of ***691*** adverse event reports that should have been filed earlier. ***This community apparently would rather cover up its errors than address them through established procedures.***

And it has been well documented that institutional review boards cannot be trusted to ensure that rules & regulations are obeyed and that experiments are scientifically & ethically sound. GAO and the Inspector General at HHS have found that the boards were understaffed; filled with conflicts of interest; failing to conduct thorough or ongoing reviews of research; and, failing to establish educational requirements for members. They actually found instances in which scientists on review boards were sitting in judgment of their own projects! It almost seems as though membership on a properly functioning board would be a full-time job. And I just don't think colleagues at the same institution can be trusted to police one another.

And what has the Office of Protection from Research Risks been doing? It is very apparent that NIH has done what it could to ***minimize the effectiveness*** of OPRR. The Director of OPRR should be a senior level executive, not a GS-15. And, according to the Washington Post, OPRR has a budget of only $2.6 ***m***illion (the NIH budget is $15.6 ***b***illion) and one full-time investigator to cover every 4,000 research organizations receiving NIH money. How much can be expected from an agency that has so few resources and so little clout? Clearly, OPRR has been treated as the proverbial stepchild within the NIH family.

SO WHAT'S THE SOLUTION?

Upgrading the status of OPRR is obviously required. But let's be realistic: how effective can a centralized office be when the research is conducted in thousands of institutions scattered across the country?

In my opinion, the quickest, least expensive, and possibly most effective course of action is for each researcher to realize that violations of guidelines, regulations, and procedures will have ***very serious*** consequences. Make the penalties for noncompliance so punitive that few scientists would risk incurring a violation. For example, a principal investigator who fails to file a timely and accurate adverse event report might be suspended from the project for one year. Allow the project to continue under someone else's leadership, but remove the person responsible for reporting the violation.

The following message has to get out to the research community: federal funding for research is not an entitlement program. Federal funding comes with constraints. No research project is so important that the constraints do not apply to it. And, failure to comply will have serious consequences.

Thank you for the opportunity to express my concerns and opinions.

Mr. MICA. Without objection your entire statement will be welcome and included as part of the record, and we did leave the record open for a period of 2 weeks. I'll now recognize, and we'll come back for questions a little bit later, Mr. Charles R. McCarthy, and he's a senior research fellow, most patient one, at the Kennedy Institute of Ethics at Georgetown University. Thank you and you're recognized, sir.

Mr. MCCARTHY. Mr. Chairman, thank you. I'm honored to be able to testify before you today. I think the matters on which you're deliberating are of extraordinary importance, and I hope we can make some contribution to protecting human subjects. Your staff asked me to comment on just one aspect of the Inspector General's report; namely, recommendations concerning utilization of Data and Safety Monitoring Boards to supplement the work of IRBs. I have focused my attention almost exclusively on that issue. I will summarize here very quickly. I have submitted a longer statement for the record.

Mr. MICA. Without objection, that entire statement will be included in the record.

[The prepared statement of Mr. McCarthy follows:]

Testimony

before

THE HOUSE OF REPRESENTATIVES
COMMITTEE ON GOVERNMENT REFORM

SUBCOMMITTEE ON CRIMINAL JUSTICE, DRUG POLICY AND HUMAN RESOURCES

John L. Mica, Florida
Chairman

Presented by
Charles R. McCarthy, Ph.D.
Senior Research Fellow
Kennedy Institute of Ethics
Gerogetown University

May 3, 2000

Charles R. McCarthy, Ph.D.

Mr. Chairman and distinguished members of the Committee. I am honored to have the opportunity to testify before you today concerning the April, 2000 Report of the Inspector General of the Department of Health and Human Services entitled *Protecting Human Research Subjects Status of Recommendations.* Your invitation recommended that I address my remarks primarily to the roles and responsibilities of Data and Safety Monitoring Boards (DSMBs) in the protection of Human Subjects

Allow me to introduce myself. My name is Charles R. McCarthy. Currently I am a Senior Research Fellow at the Kennedy Institute of Ethics at Georgetown University. I served as HEW liaison to the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research from 1974-1978. I served as Staff Director of HEW Secretary Califano's Ethics Advisory Board from 1978 until 1980 For fourteen years I served as the Director of the Office for Protection from Research Risks (OPRR) within the National Institutes of Health (NIH). My earliest experience with policies relating to human subjects at the NIH occurred when I was asked to draft testimony for Secretary Elliot Richardson in 1972 dealing with the tragic Public Health Service Study of Syphilis in black males in Macon County Alabama. (Erroneously referred to as the "Tuskegee Study.")

My testimony today is based largely on several kinds of experience . *First,* In the eight years since my retirement, I have served on four DSMBs. All of these Boards were created by, and reported to the National Heart, Lung and Blood Institute within the National Institutes of Health. Two of the Boards have completed their work, the other two remain active. All of the Boards were both capable and conscientious. *Second,* when the National Commission for the Protection of Human Subjects completed its work in 1978, it left behind approximately 125 recommendations for upgrading policies and regulations for the protection of human subjects. For nearly three years I chaired the Public Health Service Committee that drafted the regulations that today form the basis for the Common Rule for the Protection of Human Subjects. The centerpiece of those regulations is the IRB which has responsibility for initial and continuing approval of research activities that involve human subjects.

My testimony will address the following issues:
I. The Historical origins of DSMBs.
II. DSMBs and the role that they are playing.
III. The relationship Between DSMBs and IRBs.
IV. Recommendations for future action.

I. HISTORICAL ORIGINS OF DATA AND SAFETY MONITORING BOARDS

So far as I am able to determine, the first committees for tracking data pertinent to the safety of subjects were established by the National Heart Institute (now the National Heart Lung and Blood Institute) in the late 1960s.

Throughout most of the decade of the 1970's, the Kennedy Institute of Ethics at Georgetown University and the National Institutes of Health jointly sponsored seminars dealing with research ethics. Frequently the seminars involved Principal Investigators from the NIH or other Public Health Service agencies who described clinical research activities that presented ethical dilemmas, and trained ethicists from the Kennnedy Institute or other ethics centers who offered insights into ways that important research could be conducted in an ethical manner. The purpose of the seminars was to encourage research investigators to consult ethicists and to address ethical issues in research as an integral part of the design of research strategies. The seminars grew from a handful of participants in 1972 to several hundred participants toward the end of the decade. Among the regular participants was Dr. Robert Gordon who had a long and brilliant career as a research investigator, and who served for several years as Director of the NIH Clinical Center. Dr. Gordon had a keen interest in both the scientific design and the ethical design of clinical trials. Dr. Gordon took a leave of absence from NIH to study clinical trials under Dr. Curtis Meinert of The Johns Hopkins University. Both Drs. Meinert and Gordon were advocates of the use of double blinded [double masked] trials whenever appropriate to test new clinical interventions.. They believed that such trials often offer the best hope of medical advance in the cure and treatment of serious illness. In such studies, subjects were randomly assigned to one of two or three arms of a study. Neither investigators nor subjects knew to which arm of the study subjects were assigned.

However, Drs. Gordon and Meinert also recognized that it is very difficult to provide maximum protections for research subjects participating in such trials. Often the subjects of clinical trials have advanced disease. In a typical trial all subjects are asked to continue to use the best available standard medical treatment. In addition one arm of a study would add an experimental procedure to the standard treatment. A third arm of the study would sometimes be added to offer a second experimental procedure. The study would compare results in the cohort of subjects receiving only the standard treatment with results in the cohort of subjects receiving the standard treatment plus experimental procedure(s). Both subjects and investigators would be masked or blinded so that they could not know, until the end of the trial, which subjects were enrolled in each arm of the study. Sometimes subjects on an experimental arm of the trial showed more improvement or less morbidity than those receiving the standard treatment alone. Sometimes the reverse was true. Adverse events could be caused by the disease from which subjects were suffering, from experimental interventions, or from standard treatments. Collecting and comparing data from subjects on all arms of a trial provided experts with insight into the cause (and sometimes the prevention) of the adverse events.

In order to protect subjects in blinded trials, Drs. Gordon and Meinert recommended creation of a group of experts who had no vested interest in the outcome of the trial, and who were unblinded [unmasked] so that they could review the progress of the trial. In order to do so, the experts would: (1) have access to all data (particularly adverse event data) pertaining to each subject in the trial; (2) establish 'stopping rules' to be applied in the event that subjects on one arm of the study fared much better or much worse than subjects on the other arm(s) of the study; (3) be

authorized to recommend changes in the study design in order to reduce risks to subjects; and, (4) be authorized to update consent procedures to include risks or benefits that were not initially foreseen.

Dr. Gordon presented the notion of an oversight committee to the NIH/Kennedy Institute seminars on the ethical conduct of clinical trials. So far as I know, he was the first person to use the name "Data and Safety Monitoring Board" (DSMB) to describe the responsibility of the oversight bodies. He argued persuasively that DSMBs would be particularly effective for large, multi centered trials in which each participating research center saw only a small number of study subjects.

Dr. Gordon also recommended to the Public Health Service drafting committee that DSMBs be included in the regulations being proposed in response to the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The National Commission offered no direct recommendations concerning DSMBs.

The drafting committee was favorably impressed with Dr. Gordon's arguments, but the drafting committee was also aware of the fact that the National Commission had deliberated on the issues associated with protecting the rights and safety of human subjects for four years, and had made no recommendations concerning creation of DSMBs. The concept of a DSMB seemed to be a good one, but the role of the DSMB had not yet been widely tested in practice. Consequently the drafting committee added the following provision to the regulations:

> *45 CFR 46.111 (a) In order to approve research covered under this policy the IRB shall determine that all of the following requirements are satisfied:*
> *....(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.*

Although the cited provision in the current regulations authorizes IRBs to require some form of Data and Safety Monitoring, it does not hold a prominent place in the regulations, and it has not been stressed in regulatory education programs.

As a consequence, I know of no instance where an IRB has made the creation of a DSMB a condition of approval of a research study. If there are such cases, they are very rare. The reasons for failure to use this authority are not hard to find: *DSMBs are very costly. They require considerable expenditure of money and talent.* In most instances, if an IRB required a proposed research study to have oversight by a DSMB the requirement would be tantamount to disapproval of the study. .

II. DSMBs AND THE ROLE THEY ARE PLAYING

Nevertheless, creation of DSMBs by research sponsors has gradually increased over the last two decades. DSMBs are most often utilized by sponsors -- especially NIH sponsors -- of large scale, multi centered, trials. Although not established by any law, and not governed by any regulations, DSMBs are now frequently utilized by NIH funding units and by private industry as well. Most of the awarding Institutes and Centers at NIH require DSMBs to monitor multi-centered trials that are expected to involve significant risks to subjects. Despite the cost, sponsors of research involving human subjects -- both governmental sponsors and private industry sponsors -- have realized that the mere reporting of adverse events to IRBs is a procedure that offers little protection to research subjects and, consequently, little defense of the sponsor against liability claims. The sophisticated analysis of such data by DSMBs provides a far better safety procedure for subjects than the mere reporting of unanalyzed adverse events to the local IRB. DSMBs nearly always function as advisory groups to the sponsors themselves. Both NIH and FDA have issued non-binding policy guidance for DSMBs. The number of trials in which DSMBs are utilized is growing each year. However, the majority of multi centered trials are not still not overseen by DSMBs.

The high cost of a central data management center and the high cost of a DSMB is gradually coming to be considered as a necessary cost of doing high-risk multi centered research. Most pharmaceutical houses require DSMBs to exercise oversight over studies where severe morbidity is expected, and where mortality is foreseen in at least some subjects. FDA encourages industrial firms who are testing drugs, devices, and biologics to create DSMBs for risky studies.

DSMBs are expensive. Honoraria for a member's service on a DSMB range from $150 per day (government honorarium) to upwards of $2000 per day (sometimes offered by pharmaceutical houses) . Typically, DSMBs include about eight members who engage in four meetings a year. (Usually two by telephone conference and two convened meetings.) Chairpersons are sometimes expected to review data on a daily or weekly basis (e.g. if the data are close to triggering a stopping rule) and to alert members if the adverse events seem unusually numerous or severe. Members typically spend one day prior to each meeting reviewing data and a second day discussing data in the meeting. Travel costs are not trivial. Data are collected and analyzed for DSMB members by trained statisticians who display the data in many ways. Data are displayed so that DSMB members can easily see which arm(s) of a trial are doing well and which are not doing as well. Adverse events are identified for subjects on each arm of the study. Data concerning adverse events are often displayed according to age of subjects, gender of subjects, seriousness of the underlying disease, and seriousness of the adverse events. Frequently they are displayed according to race or ethnicity of subjects. Often data are also displayed that identify adverse events one week, one month, six months, or a year after each subject begins to participate in the trial. Data are also displayed for each institution so that if subjects at one institution are experiencing significantly higher adverse events than those at another institution, the DSMB can

stop accrual of subjects at a given site while allowing the study to continue at other sites. Experts are often able to determine, through the use of statistical analysis, which adverse events are caused by the disease, which by standard treatments and which by experimental treatments. In some cases DSMBs can diminish adverse events by recommending changes in the research design (e.g. administration of anti-emetic drug at certain points in the study).

III. THE RELATIONSHIP BETWEEN DSMBs AND IRBs

In preparation for this hearing, I searched all of the policies issued by NIH and by FDA concerning DSMBs that I could locate on the INTERNET. I found many policy notices that have been published concerning DSMBs, but I found, with the help of Dr. Ellis in OPRR, only two citations pertaining to DSMBs that even mentions IRBs. <http://grants.nih.gov/grants/guide/notice-files/not99-107.html/> This Notice that appeared in the NIH Guide to Grants and Contracts on June 11, 1999 states in part:

> *In response to a congressional request to streamline and reduce unnecessary federal regulations that govern the conduct of extramural scientific research, the NIH recently published a report "NIH Initiative to Reduce Regulatory Burden" ... Among the five major areas of focus, the report identified the reporting of adverse events to the IRB for multi center clinical trials as burdensome and confusing.*
>
> *The DSMB monitoring function is above and beyond the oversight traditionally provided by IRBs, and as such, is particularly important for multi center trials.*

The Notice then goes on to say that: "*Investigators must submit a written summary of DSMB periodic review to their IRB.*"

Mr. Chairman, while I consider this Notice to be a step in the right direction, it is far from sufficient. This Notice does not go far enough, it has not been promulgated in a fashion that is likely to gain the attention of IRBs or investigators who conduct research involving human subjects, and it does not help the IRB to know how to respond to the information which is traditionally simply a notice that the study can proceed.

Consequently, in practice if not in theory, a serious policy anomaly has occurred. Under the Common Rule -- that is to say under Federal Regulations promulgated by the leading research departments and agencies in the government -- IRBs are responsible for reviewing and approving covered research activities involving human subjects prior to their inception and at intervals no less than once per year. But IRBs conducting continuing review do not have access to the data (at least in intelligible form) generated by large multi-centered trials. Thus IRBs have the heavy responsibility of determining whether such research may continue to be conducted, but IRBs do not have the data necessary to make a wise decision about the continuation of research. That is one major reason why IRB members often can be heard to say, "Continuing review is largely a

waste of the IRBs time and energy." I discussed the issuance of DSMB policy recently with a senior official at FDA who acknowledged that policy makers did not even think about IRBs when they were issuing recommendations for DSMBs.

IV. RECOMMENDATIONS FOR FUTURE ACTION

Mr. Chairman, I believe the time has come to begin to formulate regulations for Data and Safety Monitoring Boards that link such Boards to Institutional Review Boards. A careful process will have to be established so that DSMBs can be cost effective. I am of the opinion that in large, ongoing, multi centered trials, the DSMB can be assigned the primary role in continuing review. Thus the cost of maintaining the DSMB can be offset, in part, by reducing the role of the IRB in continuing review to the same level that it has for studies that qualify for expedited review. I take this position because I do not believe that the local IRB can conduct as careful a review of a multi centered trial as a DSMB supported by a highly skilled central data collection center.

I further believe that the commitment to confidentiality that characterizes DSMBs can be maintained even though the Chairperson of each local IRB is allowed to see and review unblinded data sets and allowed to know (on a confidential basis) the recommendations of the DSMB.

I recognize that we currently have many kinds of DSMBs because we have many different kinds of research. If DSMB Regulations are formulated, they will have to be very flexible, and probably should be field tested for a period of a year or two before they are finalized.

DSMBs should be created by regulation to reach the following objectives. DSMBs are to:

1. Ensure that risks to subjects are minimized, and that their interests are not made secondary to the goals of scientific investigation.

2. Ensure that evaluation of interim results of multi centered trials and decision-making about continuation, modification, termination of accrual and reporting of results are based on thorough statistical and medical analysis of data.

3. Ensure that the credibility of trial reports, and that the ethics of trial conduct are above reproach. That means, among other things, that all conflicts of interest and even the appearance of professional, or financial conflicts of interest are scrupulously avoided.

4. Enable studies to proceed to a carefully planned conclusion without bias by withholding interim efficacy data from sponsors, investigators, and research subjects, while maintaining the highest level of safety possible for the study. .

5. Enable local IRB chairpersons in each of the centers where the study is taking place to share in the deliberations of the DSMB or at least to see all of the data that is displayed for DSMB meetings. IRB Chairpersons should be permitted to share information with their IRBs who should be bound to the same rules of confidentiality as the DSMBs.

Mr. Chairman, on February 2 of this year Dr. LeRoy Walters, Director of the Kennedy Institute testified before The Senate Subcommittee on Public Health Chaired by Senator Frist. Dr. Walters' testimony dealt with gene therapy, but he made some recommendations that have application for all human subjects. He made some comments that about DSMBs that are similar to the position I have advocated today. I should like to submit a copy of his testimony for the record.

Mr. Chairman and members of the Committee, I am honored to be able to testify before you today. You have a copy of my prepared remarks, so I will not repeat all of that for you. Instead I will emphasize a few points that are made in greater detail in the document I have submitted to you. .

1. IRBs were initiated by the Public Health Service in 1966. They were created to deal with research projects conducted by a single investigator in a single institution with a relatively small number of subjects. IRBs are ideally suited to determine whether such studies should be initiated and whether they should be continue.

2. Data and Safety Monitoring Boards (DSMBs) were created in the late 1960s to oversee multicentered research projects involving human subjects. The theory and practice of how such Boards should work was expanded and developed through the decade of the 1970s. Drs. Robert Gordon and Curtis Meinert were major contributors to the development of DSMBs. DSMBs are created for the dual purpose of protecting the safety of human research subjects in multicentered trials and protecting the integrity of efficacy data particularly in blinded or double blinded research studies.

In multicentered blinded trials, the local Institutional Review Board (IRB) has the responsibility for approving both the initiation of the study and for approving its continuation in the local institution. However, because local investigators can report only the data pertaining to subjects at one institution, they are unable to present a full picture of adverse events or trends in the study. Data from each research center are aggregated by a central data collection agency. Aggregated data are rarely, if ever, made available to the local IRB. Consequently, the local IRB rarely has sufficient data to determine whether a trial should continue. Usually the IRB has adverse event data about some of the subjects in the trial, but such data are not linked to individual subjects. IRBs do not know the age, the gender, the ethnic background, or the previous condition of subjects who experience adverse events. Most important, they do not know to which treatment arm the subjects who experienced the adverse events are assigned. Consequently, their judgments

cant be very conscientious, but very flawed.

DSMBs on the other hand see all of the data in a trial, and they are able to see it displayed according to age, gender, previous conditions of subjects, on which arm of the study the subject is assigned, and how the subject responded to treatment of the adverse event. Adverse events for DSMBs are classified by statisticians into very serious, moderately serious, and serious levels. They are also classified into categories of expected or unexpected events. Thus DSMBs, usually created by sponsors of the trial, are well situated to determine whether a trial should continue.

But DSMBs are pledged to confidentiality. They rarely share their information with IRBs. Consequently, we have a situation where the IRB has the responsibility to make the decision whether a trial should be continued as it is, modified, or discontinued, but it does not have the best available information on which to base that decision.

DSMBs, on the other hand, are not created by regulation. They exist for only a minority of multicentered trials, and they are advisory to sponsors. Where they exist, they have the best available information to make a sound judgment whether a trial should be continued, modified or discontinued, but under the regulations they do not have the responsibility to do so. Thus DSMBs have the best information, but lack legal authority, the IRBs have the authority but lack much of the best available information on which to base their decisions..

I therefore submit to you that DSMBs should be created by regulation to reach the following objectives:

1. Ensure that risks to subjects are minimized, and that their interests are never made secondary to the goals of scientific investigation.

2. Ensure that evaluation of interim results of multi centered trials, and decisions concerning continuation, modification, or termination of studies are based on through statistical and medical analysis of all relevant data.

3. Ensure that the credibility of trial results and the ethics of trial conduct are above reproach. That means, among other things, that the trial is well-designed and that it is modified, if necessary in the light of sound evidence, and that conflicts of interest and even the appearance of conflicts of interest are scrupulously avoided.

4. Ensure that each study proceeds to a carefully planned conclusion, without bias, by maintaining confidentiality of efficacy data, while at the same time maintaining the highest level of safety possible for the study.

5. Enable local IRB chairpersons in each center where a multicentered study is conducted to share in the deliberations of the DSMB, or at least to review all of the data available to the DSMBs. IRB chairpersons should be authorized to share information with their local IRB members who should be bound to the same rules of confidentiality as those that govern the DSMBs.

Finally, Mr. Chairman, with the help of Dr. Walters and the Library of the Kennedy Institute of Ethics I have identified six documents that recommend establishment of DSMBs to supplement the oversight of IRBs. Some of them are related only to gene therapy studies, others to cancer studies, and some to all multicentered trials. With your permission, I should like to submit them, or excerpts from them, for the record.

They are:

(1) Excerpts from the report on : *Review of the Fialuridine (FIAU) Clinical Trials* published by the INSTITUTE OF MEDICINE of the National Academy of Sciences in 1995.

(2) Excerpts from : *Clinical Trials Cooperative Group Program Guidelines*, dated August of 1996.

(3) *Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials*, dated June 11, 1999.

(4) A statement delivered by LeRoy Walters, Ph.D, before. the Senate Subcommittee on Public Health Chaired by Senator Bill Frist, M.D. On February 2, 2000.

(5) A letter, with attachments, from Senator Edward M. (Ted) Kennedy to Honorable Donna Shalala, Secretary, HHS dated March 6, 2000.

(6) A press release dated March 7, 2000 issued jointly by NIH and FDA recommending that universities and other research institutions that sponsor gene therapy trials develop and submit monitoring plans for their studies.

In closing, let me say that I believe that protections for human research subjects is a matter of high national need and importance. I commend this Committee for holding a hearing on this topic. Let us hope that the partnership between the biomedical research community and the United States government will continue to make progress in improving human health and well-being while maintaining the world's best protections for the rights and welfare of human research subjects whose dedication and generosity make such progress possible.

I will be pleased to answer any questions that you or other Committee members may have.

Review of the Fialuridine (FIAU) Clinical Trials

Committee to Review the Fialuridine (FIAU/FIAC) Clinical Trials

Division of Health Sciences Policy

INSTITUTE OF MEDICINE

Frederick J. Manning and Morton Swartz, *Editors*

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anticipate this unfortunate event. We would nevertheless urge the readers of this report to put this tragedy in a proper perspective as a distinctly rare occurrence, related to a previously unrecognized form of late drug toxicity, in a field with an otherwise exemplary safety record.

On the basis of its review of the FIAU studies, the IOM committee will make some recommendations on the future conduct of early phase drug trials. Although the IOM committee's recommendations are focused on Phase I and Phase II trials, they do not stem from perceived deficiencies in the conduct of the investigators or sponsors in the FIAU studies; as already noted, none were identified. The IOM committee believes that implementation of its recommendations *may* reduce the already very low probability of occurrence of toxicity of the sort there was in the fialuridine studies, particularly when studying drugs that are similar to fialuridine in structure or action. In many instances the effect will be to insure the continued and consistent use of procedures and practices employed in the FIAU trials reviewed here.

RECOMMENDATIONS

Generic Issues

1. Proceed cautiously in revision of the current drug development system. The current system has evolved checks and balances that have benefited new drug development and patient safety, and no single component can undergo a major revision without endangering the system as a whole. The committee is doubtful that any of the changes reviewed above and/or proposed below, had they been in effect prior to the initiation of the FIAC/FIAU trials reviewed here, would have substantially altered the tragic outcome.

2. All clinical researchers engaged in trials should be exposed to explicit training not only on the design and conduct of clinical trials and their ethical obligations to patients but also on their legal and regulatory obligations to both the sponsor and the FDA.

3. We urge the establishment of a system of no-fault compensation for research injury by government, sponsor or some combination of both.

Trial Design

4. Some form of independent safety monitoring would be a valuable component of any clinical trial in which patients are treated for extended periods, but they are especially important for all double-blind trials and in any trial in which there is reason to anticipate that evidence of adverse reactions could be confused with evidence of disease progression or therapeutic response. For other types of trials the sponsor should bear the burden of demonstrating that a monitor is unnecessary.

5. We support in principle the desirability of controls in Phase II studies, even while recognizing that statistical power will generally be inadequate to detect all but the most common of adverse drug effects, and among those, only those that rarely occur in untreated subjects. Nevertheless, particularly in trials involving extended treatment of patients, the use

of some concurrent comparison group should help focus attention on the importance of differentiating drug effects from the underlying disease(s).

6. Research into the development of a database from which to construct historical control groups should also be supported. Such control groups may be needed as comparison groups when suitably matched concurrent control groups are not feasible. The extensive data submitted to the FDA through the IND process are a potentially valuable resource to custom match patients in new drug trials with controls from previous trials, matching not only for entry criteria but also for disease extent and severity, concomitant medications and other confounding variables.

7. Concerted efforts should be made to include in all clinical trial protocols explicit prospective criteria to help distinguish between adverse events related to drug treatment and changes in the underlying disease, for better or worse, whether or not controls are employed.

8. Clinical protocols should also have a section explicitly addressing the determination of the followup period, based on preclinical data and clinical data from other drugs thought to be similar in structure and action. Drugs suspected of modifying DNA or associated macromolecules demand a minimum of 6 months followup.

9. At the outset of extended Phase II trials, consideration should be given as to whether there is sufficient evidence of safety to justify simultaneous enrollment of a substantial group of patients, or whether the patients' disease is so serious that access to the drug seems warranted.

Adverse Event Reporting

10. Data should ideally be analyzed (by the investigators or independent safety monitor in Phase I and Phase II trials, and by data safety monitoring committees or data coordinating centers in multicenter Phase III studies) on a continuing real-time basis rather than only after all case report forms are complete for all patients. This will ensure that the fewest possible patients are exposed to possible hazards, and that rapid intervention will prevent or limit injury to individual patients.

11. We concur with the suggestion of the FDA Task Force that some form of cumulative adverse event reporting should be provided by the sponsor, in a form which includes not only those events previously reported as serious, unexpected and drug related, but also any events judged to have met only the first or the first two of those conditions, along with the sponsor's explanation of the event. A careful analysis of all available information rather than a "worst case" assumption should then determine further actions.

12. We believe that requiring a cumulative and all-encompassing report of the sort referred to in the previous recommendation every six months will prove to be a substantial impediment to development of drugs to combat life-threatening diseases (e.g., cancer) where adverse events are frequent because of the often progressive nature of the underlying disease. Some judgement will always be necessary, by the investigators deciding the most likely cause of adverse events, and by the FDA, in deciding for which drugs and at what intervals a cumulative safety summary is necessary. Ideally the investigators and the FDA would work together in making both of these determinations.

CLINICAL TRIALS COOPERATIVE GROUP PROGRAM GUIDELINES, AUGUST 1996

V. QUALITY CONTROL, STUDY MONITORING, INDEPENDENT DATA AND SAFETY MONITORING COMMITTEES AND ON-SITE AUDITS

[V.1. Background and Definitions] [V.2. Quality Control] [V.3. Study Monitoring]

[V.4. Data and Safety Monitoring Committees] [On-Site Audit Program]

V.1. BACKGROUND AND DEFINITIONS

The multi-center nature of Group trials presents a variety of challenging methodologic problems regarding assurance of quality and consistency in study conduct. The need for formal mechanisms of medical review and quality control is obvious and Groups have developed a number of approaches to these issues.

In addition there are special problems in assuring the safety of individual patients participating in each study, in maximizing their likelihood of exposure to optimal treatment, and in general, ensuring that the interests of patient participants are not subsidiary to those of the scientific investigation. The continual assessment of the progress of studies necessary to achieve these ends is referred to in this document as study monitoring.

A related need is for verification of the accuracy of data submitted from individual investigators to the Group. This need overlaps considerably with the obligation of the DCTD as a sponsor of investigational agents to visit each site where investigational agents are studied, for the specific purpose of: 1) auditing medical records, and 2) assuring compliance with regulatory requirements of the FDA, including appropriate storage and handling of investigational agents. Each Group is therefore required to establish a system of periodic on-site audits of each performance site, with CTEP oversight of the audit program. This dual responsibility of the Groups and the DCTD is referred to as the on-site audit program. (see the NCICTMB Guidelines for Onsite Monitoring of Clinical Trials for Cooperative Groups and CCOP Research Bases.)

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V.2. QUALITY CONTROL

Quality control is a complex topic spanning the entire range of diagnostic and therapeutic modalities employed by each Group. Generalization concerning optimal quality control is impossible. Cost and benefit are obviously important factors in this assessment. Examples of the kinds of considerations to be applied follow:

1. Radiation therapy quality control may involve either simultaneous (rapid turnaround) or

retrospective review of port films and compliance with protocol-specified doses for individual patients. Minimal standards for acceptability of equipment may be required. Each radiation therapy facility that treats patients on Group studies undergoes periodic physics review and equipment calibration by the Radiological Physics Center (RPC). The RPC in Houston, TX also supplies each Group's radiation therapy quality control office with the physics data necessary to conduct its case-level review.

2. Chemotherapy quality control is usually carried out through retrospective review of submitted flow sheets, with determination of protocol compliance in dose administration and dosage modification. The criteria vary considerably from study to study and from Group to Group and depend heavily on the specific research questions addressed.
3. Surgical quality control includes assessment by surgeons of the adequacy of protocol-specified surgical procedures through review of the operative notes, study-specific surgical forms, and pathology reports. Standards of acceptability for specialized surgical equipment, or requirements for participation in workshops may be necessary in some instances. Where appropriate, surgical modality committees may wish to draft handbooks of acceptable guidelines for surgical procedures used in studies.
4. Pathology review is usually retrospective and may be either by a committee within the Group or by an external reference panel. Pathology review is not mandated by CTEP for all cases, but should be required by the Group when known variability in the accuracy of histologic diagnosis is a potentially serious problem or when pathology data may provide important prognostic information.
5. Appropriate quality control for other therapeutic and diagnostic modalities is as essential to good data quality as those described above. Standardization of decentralized laboratory procedures (e.g., hormone receptor determinations) is an important case in point.

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V.3. STUDY MONITORING

All clinical treatment research carries with it the obligation to ensure optimal therapy for participating patients, and optimal conduct of the research such that the patients' participation is meaningful. In this context accurate and timely knowledge of the progress of each study is a critical Group responsibility and includes the following:

1. Precise tracking of patient accrual to individual studies and the mechanisms to ensure adherence to defined accrual goals;
2. Ongoing assessment of patient eligibility and evaluability and correction of specific problems in this regard;
3. Adequate measures to ensure timely submission of protocol-required data for individual patients;
4. Adequate measures to ensure timely medical review and assessment of these individual patients' data;
5. Rapid reporting of treatment-related morbidity in individual patients and measures to ensure communication of this information to all parties to whom it is important;
6. Prompt assessment of the significance of such information in the context of the entire study's experience;
7. Interim evaluation and consideration of measures of outcome (although to the extent consistent with patient safety and good clinical trials practice such interim analyses should be minimized in

frequency; access by participating investigators to interim outcome data should be limited as much as possible; see V.4., Independent Data Monitoring Committees.)

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V.4. DATA AND SAFETY MONITORING COMMITTEES

For Phase III trials, Groups are required to establish data and safety monitoring committees (DSMCs) that are independent of study leadership, are clearly free of conflicts of interest, and have formally documented policies and procedures which are approved by NCI. The main objectives of the DSMC are to:

1. Ensure that patients in the trial are protected and that their interests are not made secondary to the interests of scientific investigations.
2. Ensure that evaluation of interim results and decision making about continuation, modification, termination of accrual and reporting of results are made competently based on thorough evaluation.
3. Ensure that the credibility of trial reports and ethics of trial conduct are above reproach with no possible appearance of professional or financial conflicts of interest.
4. a. Enable physicians entering patients to remain free of knowledge of interim efficacy data. This permits physicians to continue to approach their patients honestly and avoids the need to modify informed consent based on non-statistically-significant interim results.
5. b. Enable study leadership to remain free of knowledge of interim efficacy data so that they may deal honestly with their peers in encouraging them to enter patients in the study and so that they do not put themselves, or the study, at risk by indirectly divulging interim results.

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V.5 ON-SITE AUDIT PROGRAM

V.5.A. Purposes

As a sponsor for investigational new agents, the DCTD is required by FDA regulations to maintain an on-site audit program. Through formal agreements with the FDA, the DCTD has delegated much of this responsibility to the Cooperative Groups, although CTEP oversees the program. The specific purposes of the audit programs are to document the accuracy of data submitted to the Cooperative Group, and to verify investigator compliance with protocol and regulatory requirements for all clinical investigations.

V.5.B. Patient Case Reviews

By comparison of submitted data with information contained in the patient's actual medical records, this component of the on-site audit program seeks to assure accuracy and completeness of Group information integral to the assessment of:

a. Patient eligibility;

b. Compliance with protocol-defined therapy;

c. Tumor response;

d. Treatment related toxicity;

e. Protocol-required laboratory and diagnostic evaluations;

f. Overall quality of record keeping;

g. Concomitant therapy or other information which might affect study results but is not recorded on submitted study forms.

V.5.C. Regulatory Requirements

This component of the on-site audit program is intended to assess:

a. Documentation of Institutional Review Board (IRB) approvals, reapprovals, and protocol amendments;

b. Documentation of an IRBapproved, properly signed and dated informed consent document for each case audited, that includes an adequate description of the rules and benefits as contained in the model informed consent submitted to the NCI;

c. Security of investigational drug handling;

d. Adequacy of NCI drug accountability records (DAR).

V.5.D. Procedures

Each Cooperative Group must establish and follow an on-site audit program and audit procedures, in accordance with guidelines provided by and available from the Clinical Trials Monitoring Branch (CTMB), CTEP ("NCI-CTMB Guidelines for On-Site Monitoring of Clinical Trials for Cooperative Groups and CCOP Research Bases"). Each institution must be visited at least once every 36 months but remains at yearly risk of an audit. Audits are conducted by Group peers, but a percentage of institutions will be co-site visited by CTEP CTMB staff or their agents. Protocols to be reviewed are selected by the Group's Statistical and or Headquarters office in accordance with the above guidelines. A sample of investigational agent studies is always included when the performance site has accrued patients to such studies, as are intergroup studies. Individual cases are then randomly selected by the Statistical and/or Headquarters office for review.

A preliminary audit report is to be FAXed to CTMB within one working day of the audit. A final report of each audit is sent by the Group to CTMB within ten weeks of the audit. CTMB staff review the audit findings as well as the Group's evaluation and response.

V.5.E. Group Evaluation and Response

The discovery of actual fraud or other serious research misconduct during a Group audit has been

rare. On the other hand, problems covering a wide spectrum of severity and type are often found. Most are appropriately dealt with by constructive suggestions and are easily remedied through education of investigators and data managers. NCI follow-up is required in the event of findings suggestive of intentional misrepresentation of data and/or disregard for regulatory safeguards, as well as other matters of sufficient seriousness. In such instances, the NCI/CTMB staff should be notified by telephone immediately, since other Federal agencies may require notification. Procedures for immediate suspension of accrual at the performance site may be required.

After reviewing the audit report and the Group's response, the CTMB staff may require further action such as a written corrective plan submitted by the institution or a repeat audit within a shorter interval than 36 months. In cases of suspected fraud or other serious problem of compliance with regulatory requirements, CTEP may request formal investigation by the US Public Health Service, the FDA, and/or the Justice Department.

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http://grants.nih.gov/grants/guide/notice-files/not99-107.htm

GUIDANCE ON REPORTING ADVERSE EVENTS TO INSTITUTIONAL REVIEW BOARDS FOR NIH-SUPPORTED MULTICENTER CLINICAL TRIALS

Release Date: June 11, 1999

National Institutes of Health

Effective July 1, all multi-site trials with data safety monitoring boards are expected to forward summary reports of adverse events to each IRB involved in the study. This action in no way reduces the responsibilities of individual IRBs to address such reports coming to them from the site over which they have responsibility. NIH program staff will ensure that this language appears in new solicitations for clinical trials and is broadly disseminated to current principal investigators with appropriate follow-up.

This National Institutes of Health (NIH) document provides guidance to investigators engaged in NIH-supported multi-center clinical trials to promote effective reporting of adverse events to the appropriate IRBs. The mechanism for reporting should be optimized to protect study participants from research risks, while at the same time reducing the regulatory burden on these committees. It is recognized that multiple parties, e.g., NIH, Food and Drug Administration (FDA), or industrial sponsors, must be notified of adverse events. However, this document provides guidance specifically for IRB notification. The NIH is directing principal investigators to report adverse events by identifying the DSMB to the IRB and ensuring reports of assessments of adverse events are transmitted from the DSMB to each IRB.

Background

In response to a congressional request to streamline and reduce unnecessary Federal regulations that govern the conduct of extramural scientific research, the NIH recently published a report "NIH Initiative to Reduce Regulatory Burden" following extensive interviews and focus group meetings with the research community (http://grants.nih.gov/grants/policy/regulatoryburden/index.htm). Among the five major areas of focus, the report identified the reporting of adverse events to the IRB for multicenter clinical trials as burdensome and confusing. Some of the confusion stems from the different regulations governing the NIH and the FDA in this area.

Federal regulations (45 CFR Part 46, Subpart A), shared by 17 Departments and Agencies as the Common Rule, require written procedures and policies for ensuring reporting of "unanticipated problems" involving risks to participants to the IRB, appropriate institutional officials, and the Department or Agency Head. Under a different set of regulations, 21 CFR 312, the FDA requires the sponsor to notify the FDA and participating investigators of any adverse event associated with the use of a test article that is "both serious and unexpected." The reporting of adverse events is in addition to, and does not supplant, periodic reports to the IRB at intervals appropriate to the degree of risk in the study, generally, an annual report.

Definitions

The definitions and reporting requirements for adverse events differ between the two Federal regulations. The notification requirements described in the Common Rule define adverse events as "unanticipated problems" involving risks to study participants or others. Generally, the funding Institutes and Centers establish operational definitions of adverse events that apply to the particular trial. The National Cancer Institute (NCI), for example, defines adverse drug reactions in its clinical trials involving antineoplastic agents, as: (1) previously

clinical trials involving antineoplastic agents, as: (1) previously unknown toxicities; and (2) life-threatening or fatal toxicities regardless of whether or not previously unknown. Toxicity criteria are generally included in the protocols.

The FDA, in Federal regulations 21 CFR Part 312, defines adverse events as any untoward medical occurrence that may present itself during treatment or administration with a pharmaceutical product, and which may or may not have a causal relationship with the treatment. In the guideline entitled "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting", the Agency further clarifies and defines serious adverse events stemming from a drug study as any untoward medical occurrence that at any dose results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; creates persistent or significant disability/incapacity, or a congenital anomaly/birth defects (http://www.fda.gov/cder/guidance/iche3.pdf).

Issues

For multicenter clinical trials, an IRB may receive individual adverse event reports from sites other than its own. Such off-site reports may not be presented in a useful format and duplicate reports are received, sometimes, months apart. The receipt of reports that are not aggregated (no numerators or denominators are included) and that come from disparate sources contributes to confusion and added workload of the IRB. More importantly, the format of the reports jeopardizes the IRB's ability to make an informed judgement on the appropriate action, if any, to be taken.

Investigator Responsibility

An investigator is responsible for knowing the policies of the local IRB, adhering to these policies, and maintaining a copy of the policies in the study file. An investigator is also responsible for the accurate documentation, investigation and follow-up of all possible study-related adverse events. For NIH-supported multicenter clinical trials, investigators do not necessarily report these events to off-site IRBs as long as the local IRB has been notified. In lieu of receiving individual adverse event reports from each of the clinical sites, the IRBs should receive from the investigator a written summary report whenever a data safety monitoring board (DSMB) review has taken place (see below). It should be noted that these summary reports do not replace other reporting requirements to the local IRBs, e.g., annual reports.

Any protocol submitted for IRB approval should both identify the DSMB (not members' names), if any, that will be reviewing interim results, and include a brief description of the monitoring plan as well as procedures for transmitting the DSMB's summary reports to the IRB.

Communication between Data Safety Monitoring Board and IRB

DSMBs play an essential role in protecting the safety of participants, and assuring integrity of the study. They accomplish the former by being familiar with the protocol, proposing appropriate analyses, and periodically reviewing the developing outcome and safety data. They accomplish the latter by reviewing data on such aspects as participant enrollment, site visits, study procedures, forms completion, data quality, losses to follow-up, and other measures of adherence to protocol. The Board makes recommendations based on those data, regarding appropriate protocol and operational changes. DSMBs (and the investigators) monitor toxicity and discuss any concern in this regard. The DSMB monitoring function is above and beyond the oversight traditionally provided by IRBs and as such is particularly important

traditionally provided by IRBs and as such is particularly important for multicenter trials.

Typically, the study statisticians and the investigators, along with the DSMB, develop monitoring guidelines. However, for some trials, the study statisticians and the investigators develop interim monitoring guidelines that are reviewed as part of the protocol review process by the Institutes and Centers.

In the recent re-issuance of the policy for data and safety monitoring (NIH Guide for Grants and Contracts, June 12, 1998), the NIH clearly addressed the need for communication between the DSMB and IRB. Once a DSMB is established, each IRB should be informed of the operating procedures with regard to data and safety monitoring (e.g., who, what, when, and how monitoring will take place). This information will serve to assure the IRB that the safety of the research participants is appropriately monitored. If the IRB is not satisfied with the monitoring procedures, it should request modifications. While it is recognized that it may not be possible to satisfy every IRB completely, IRB comments should be considered seriously.

The DSMB's summary report should provide feedback at regular and defined intervals to the IRBs. The Institutes and Centers should assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. For example, after each meeting of the DSMB, the executive secretary should send a brief summary report to each investigator. The report should document that a review of data and outcomes across all centers took place on a given date. It should summarize the Board's review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It should also inform investigators of the study the Board's conclusion with respect to progress or need for modification of the protocol. The investigator is required to transmit the report to the local IRB.

IRB Responsibilities

An IRB has the authority to suspend or terminate approval of research at its site that has been associated with unexpected serious harm to participants. When an IRB takes such action, it is required to provide a statement of reasons for the action and to promptly report this action to the investigator, appropriate institutional officials, the Department or Agency head, Office for Protection from Research Risks (OPRR), and the FDA if an investigational new drug or device is involved. For studies that have a DSMB, the investigator should forward summary reports to the IRB as soon as they are received; it is within the purview of the IRB to request this information. IRBs could make reporting contingent on IRB approval for specific studies that are deemed appropriate. An IRB should communicate concerns to the DSMB and/or the Institute sponsoring the study if it believes that the safety of study participants is in jeopardy.

Implementation:

The NIH program staff will review multicenter clinical trials with the following expectations:

A. Investigators submitting a protocol for IRB review must identify the DSMB involved, if any. They must describe plans for monitoring adverse events.

B. Investigators must submit a written summary of DSMB periodic review to their IRB.

C. When a study is conducted in multiple sites, the funding Institutes and Centers must assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRBs.

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STATEMENT BEFORE THE SUBCOMMITTEE ON PUBLIC HEALTH

SENATE COMMITTEE ON HEALTH, EDUCATION, LABOR, AND

PENSIONS

CHAIRMAN: BILL FRIST, M.D.

February 2, 2000

LeRoy Walters, Ph.D.

Director, Kennedy Institute of Ethics

Georgetown University

Washington, D.C.

Mr. Chairman and Members of the Subcommittee:

Thank you for inviting me to discuss ethical issues in human-gene-therapy research. I appreciate the opportunity to be a participant in this important hearing.

My name is LeRoy Walters. I have been a faculty member at the Joseph and Rose Kennedy Institute of Ethics (as it is now called) at Georgetown University since 1971. It has been my privilege to be a member of the NIH Recombinant DNA Advisory Committee (RAC) on three separate occasions – from 1976 to 1980, from 1984 to 1988, and from 1992 to 1996. From the beginning of 1993 to the end of 1996, I served as Chair of the RAC. I have had a long-standing interest in the ethical issues surrounding gene-therapy research. In

1997 a coauthor, Julie Gage Palmer, and I published a book entitled *The Ethics of Human Gene Therapy.*

Two Eras in the Early History and Work of the NIH Recombinant DNA Advisory Committee (RAC): 1974-1983 and 1984-1990

The NIH RAC has had a long and distinguished history. It was initially established in the fall of 1974, shortly before the Asilomar meeting on research with recombinant DNA. The committee met for the first time in February of 1975, immediately after the Asilomar meeting. From that moment until the early 1980s the RAC set the safety standards for all recombinant DNA research being conducted in the United States. These standards became known as the NIH "Guidelines for Research Involving Recombinant DNA Molecules." The NIH guidelines were adopted, in whole or in part, by many other industrialized countries.

In the early years most recombinant DNA research was funded by NIH and NSF, so academic researchers had little choice but to follow the "Guidelines." However, private companies also voluntarily complied with the RAC's guidelines, in part to avoid regulation by their states or municipalities. While Congress considered numerous bills that would have regulated recombinant DNA research, especially in 1977, in the end the Congress deferred to the NIH and the RAC.

By about 1980, it was clear that most kinds of laboratory research with recombinant DNA were safe for both laboratory workers and the environment.

New questions arose, such as the use of recombinant DNA techniques for large-scale production of human insulin and the deliberate release of recombinant DNA into the environment, for example, to lower the temperature at which strawberry plants freeze. These new technologies gradually moved to the appropriate regulatory agencies, the Food and Drug Administration and the Environmental Protection Agency.

By 1983 it seemed as if the RAC's advisory role might no longer be needed. By a strange and perhaps fortuitous quirk of history, a new technique called "human gene therapy" was just beginning to be developed. There was a certain degree of continuity with the past. After all, gene therapy was, from one perspective, the introduction of recombinant DNA (or products derived from recombinant DNA) into human beings. However, gene-therapy research was clearly a hybrid field. On the one hand, it was highly technical and required the expertise of molecular biologists and human geneticists. On the other hand, gene-therapy research was human-subjects research, which was governed by its own set of rules and which was quite comprehensible to laypeople.

In 1982 a report by a presidential commission on bioethics, *Splicing Life*, and a congressional hearing on "Human Genetic Engineering" had framed the major ethical issues in gene-therapy research. In response to those hearings, the NIH and the RAC began in 1983 to consider whether the committee should volunteer to review gene-therapy research protocols on a case-by-case basis. Over

the course of a year the NIH and the RAC moved step-by-step toward accepting the oversight of gene-therapy research, in part because its other work was essentially finished and in part because no other agency or committee was prepared at that time to review this emerging field of research. A working group on human gene therapy was established during the summer of 1984 as a subcommittee to the RAC, and this working group began developing guidelines for gene-therapy research in the fall of that year. (I was privileged to chair that working group from 1984 to 1991.) Once again, the Congress deferred to the executive branch and to its public advisory committee, the RAC. It did not pass legislation regulating gene-therapy research, nor did it establish a presidential advisory committee on the "Human Applications of Genetic Engineering," as recommended by Congressman Albert Gore, Jr., in H.R. 2788 (April 27, 1983). The Congressional Office of Technology Assessment also published a report in late 1984, *Human Gene Therapy: Background Paper*, that seemed to accept the merits of the approach being taken by NIH and the RAC.

What were the central ethical questions to be asked about any proposed gene-therapy research protocol? In my view, the many questions asked in the RAC's guidelines – the "Points to Consider" document – can be reduced to four rather simple and straightforward questions:

1. What are the potential harms and benefits of the research to the research subjects who will participate in a planned study?

2. How will these potential harms and benefits be communicated to prospective research subjects, so that they can make voluntary and informed decisions about whether to participate in the research?

3. How will the selection among potential research subjects be made in a fair and equitable way, especially in cases where more people want to participate than can be enrolled in a study?

4. How will the privacy of research subjects be protected and the confidentiality of their medical information preserved?

If it is possible to develop guidelines for an emerging field of biomedical research too early, the RAC and its working group did so. We hurried to finish polishing the "Points to Consider" document in the spring and summer of 1985, then had to wait for almost two years for even a "preclinical" gene-therapy protocol. In the summer and fall of 1988, the first gene-marking study was reviewed and approved by the working group and the parent committee. Finally, in 1990, two gene-therapy studies were reviewed and approved. On September 14, 1990, the first officially-sanctioned gene-therapy study began when W. French Anderson, R. Michael Blaese, and their colleagues administered genetically-modified T-cells to a four-year-old girl named Ashanti DeSilva.

In its guideline-writing efforts and its review of the earliest preclinical and clinical protocols the RAC was supported by a series of excellent NIH staff people in an office called the Office of Recombinant DNA Activities (ORDA). The

professionalism of this staff, its commitment to the public health and the protection of human subjects, and the long tenure of many of its members have all contributed significantly to any success that the RAC may have had in its oversight responsibilities over the years.

The Years 1991 to 1995: Parallel Efforts by the NIH and the FDA

Gene-therapy research "took off" between 1991 and 1995, and the RAC was hard-pressed to review the many protocols that it received, especially during the latter years. In preparation for its June 1995 RAC meeting, RAC members and the ORDA staff undertook a comprehensive review of gene-therapy and gene-marking studies that had been reviewed and approved to date. This review, which was published in *Human Gene Therapy* on September 10th, 1996, revealed that during the first four years of intensive gene-therapy research there were hints of benefit in several studies but that in no case had a patient been cured of his or her disease by this new experimental approach.

In the early 1990s the Food and Drug Administration also greatly enhanced its capability to review Investigational New Drug (IND) applications that employed gene-therapy techniques. FDA officials and reviewers regularly attended RAC meetings and increasingly participated in RAC discussions. Researchers began to note differences in the kinds of information being sought by the RAC and the FDA, and some researchers also complained that they had to

jump over two regulatory hurdles rather than one.

In response to these complaints and similar complaints by some AIDS activists and biotechnology companies, the NIH and the FDA sought, in 1994, to work out a system of dual submission of protocols and coordinated review. In retrospect, it seems quite clear that this well-meaning effort did not go far enough and that serious differences in emphasis and approach remained between the NIH and its advisory committee, the RAC, on the one hand, and the FDA, on the other. The two agencies also failed to agree on how to develop a data-management system for gene-therapy research.

September 1995 and December 1995: the Verma Committee Report and the Orkin-Motulsky Committee Report

In September 1995 a committee chaired by Inder Verma submitted recommendations to NIH Director Harold Varmus regarding the appropriate role of the RAC in the review of gene-therapy research. The committee concluded that the RAC had an important ongoing role in the review of such research but recommended that the RAC publicly review only research protocols that raised novel questions, for example, protocols that employed a new vector or sought to treat a new disease. For all other protocols, those that did not raise novel questions, the Verma Committee recommended that the review be conducted solely by the FDA.

In December 1995 a committee chaired by Stuart Orkin and Arno Motulsky delivered a somber verdict on the first five years of publicly-reviewed and -approved gene-therapy research: Not a single study had demonstrated clinical benefit to patients from gene therapy alone. The committee recommended that more attention be paid to the infrastructure for gene-therapy research, including the development of better vectors and of a better understanding of human immunology.

Eighteen Months of Uncertainty: May 1996 to October 1997

In May of 1996 NIH Director Harold Varmus announced his intention to abolish the RAC in a speech delivered in Hilton Head, South Carolina. This proposal was formulated more precisely in a *Federal Register* notice published in July 1996. Over the next year and a quarter the RAC's future role was debated by academic people, patient advocacy groups, biotechnology companies, several members of Congress, and RAC members themselves. Two general revisions of the original plan were published in the *Federal Register,* the first in November 1996 and the second in February 1997. Finally, on October 31, 1997, a new oversight system for gene-therapy research was formally announced in the *Federal Register.* According to this final plan, the RAC and the NIH would no longer approve or disapprove gene-therapy research protocols. Instead, the RAC would discuss protocols that raised novel issues and make suggestions to the authors of

the protocols. It was understood by all that RAC discussions would also inform FDA reviewers in their confidential negotiations with the sponsors of gene-therapy research who had submitted the same protocols as part of the IND review process.

There are five other features of the October 1997 plan that are worthy of note. First, the Office of Recombinant DNA Activities accepted responsibility for developing a data-management system to assist the RAC in its review of adverse events and its annual audit of gene-therapy research. Second, gene-therapy researchers had a clearly-stated duty to inform ORDA and the RAC of any changes in RAC-reviewed protocols that occurred between the time of RAC review and time that the researchers received permission from FDA to proceed with their proposed research (under an IND). Third, gene-therapy researchers also had a clearly-stated duty to report "any serious adverse event" in a gene-therapy research protocol to ORDA. Fourth, researchers were required to submit Annual Data Reports to ORDA for inclusion in the data-management system and analysis by the RAC. Finally, ORDA and the RAC would plan Gene Therapy Policy Conferences to look at broad themes like genetic enhancement, in utero gene therapy, or the use of lentiviruses as vectors.

From October 1997 to the Present: How Is the New System Working?

There is some good news to report from the past two-plus years. The Gene Therapy Policy Conferences have been highly successful in promoting

interdisciplinary discussion of several important topics. RAC members continue to be deeply committed to their public roles and have been quite forthright in expressing concern about being asked to treat adverse-event reports as proprietary information. Similarly, the staff people at ORDA (recently made a part of the NIH Office of Biotechnology Activities [OBA]), have devoted long hours to fulfilling the roles assigned to them under the October 1997 agreement.

However, a series of developments from September 1999 through January 2000 have made it clear that there are serious problems in the current oversight system for gene-therapy research. My goal in enumerating these problems is not primarily to blame any individual or group of individuals, but rather to provide evidence that the oversight system as a whole is failing.

First, the data-management system, discussed and planned for since 1994, is still not available. This system is essential for the timely reporting and analysis of adverse events and for the RAC's annual review of gene-therapy research. Initially, delays occurred because of FDA's 1995 decision not to collaborate in the development of the database. In recent years ORDA has not had sufficient staff or resources to complete the development of the database.

Second, many gene-therapy researchers who are covered by the NIH "Guidelines for Research Involving Recombinant DNA Molecules" have either been oblivious to their responsibility to immediately report serious adverse events to ORDA (and thus to the RAC) or have neglected to fulfill that responsibility.

The requirement is not new. It has been included in the RAC's "Points to Consider," in one form or another, since January of 1985. One of the most disheartening statistics that I have seen during the past four months appeared in a recent letter from former NIH Director Harold Varmus, to Congressman Henry Waxman. According to Dr. Varmus, only 39 (or 5.6%) of 691 serious adverse events in gene-therapy research using adenoviral vectors had been reported to ORDA before October 1999, when NIH and FDA began a vigorous joint effort to gather and analyze those events.

Third, the lack of coordination between the NIH and the RAC, on the one hand, and the FDA, on the other, continues in certain arenas. The two parent agencies have had different histories and sometimes reflect those histories in divergent approaches to the same question. Important issues remain unclarified – for example, Is the RAC advisory to the FDA, or not? If so, does the RAC provide this advice formally or informally? Certain modes of FDA-NIH cooperation that should have been put in place by October 1997, at the latest, have only been initiated within the past two months, in response to a crisis. Here I am thinking especially of two welcome changes in FDA's standard operating procedures. In December 1999, FDA began reporting weekly to the OBA on changes to gene-therapy research protocols and on adverse-event reports from the preceding week. I cannot understand why these lines of communication were not opened years ago.

Finally, I will express a concern based on reports that I have heard from several usually-reliable sources. It is possible that the FDA itself is not adequately staffed to analyze the serious adverse events emerging from this one area of biologics research, and that its own data-management systems include only a fraction of the adverse-event information that is submitted by the sponsors of gene-therapy research. Thus, I would like to ask the FDA three quuestions - not in order to criticize but rather in the spirit of working toward a better oversight system: What percentage of the 691 serious adverse events in trials using adenovirus vectors were included in FDA's online databases before October 1999? What fraction of these events had to be retrieved from paper reports? And what fraction had not been reported to FDA at all before the vigorous joint effort of FDA and NIH to track down all such events? Even if all these adverse events were captured in online databases by the end of September 1999, a further question can be raised: Would FDA welcome the creation of an independent DATA and Safety Monitoring Board (DSMB) that would also be able to analyze and act upon reports of adverse events in gene-therapy studies?

A Response and Five Recommendations

As a nation we can do a better job of protecting the human subjects in gene-therapy studies than we have done during the past ten years. The death of a generous young man, the serious side effects experienced by several – and perhaps

numerous – other subjects, and the almost-total breakdown of the system for reporting serious adverse events to ORDA (OBA) and the RAC should be a wake-up call to us all.

How can we do a better job? In my view, five steps need to be taken.

1. The role of the RAC in the oversight of gene-therapy research should be strengthened rather than weakened. This public advisory body has a 25-year track record and a national and international reputation for integrity and independence. The RAC is one of the public's best guarantees that gene-therapy studies will be conducted in a way that respects the rights and the welfare of the courageous people who volunteer to participate in these studies. Implicit in my request for strengthening the RAC's role is an appeal to the NIH Director to restore the RAC's authority to approve and disapprove individual gene-therapy research protocols.

2. We should provide the human subjects who participate in gene-therapy research with the same kinds of protection that we provide to other subjects enrolled in multi-center clinical trials. Human subjects in AIDS trials and in the Women's Health Initiative (WHI) clinical trial enjoy the benefit of having Data and Safety Monitoring Boards (DSMBs) review the data emerging from these studies at regular intervals. The DSMBs are in a position to warn both researchers and research subjects if unexpected patterns of adverse events begin to appear. Both the NIH and the FDA have been strongly supportive of the DSMB concept.

(In fact, the Heart and Lung Institute at the NIH established the earliest DSMBs in the late 1960s.) The Institute of Medicine committee that investigated the deaths of multiple human subjects in the Fialuridine (FIAU) clinical trial also vigorously endorsed the creation of "some form of independent safety monitoring" in clinical trials. My specific suggestion is that the NIH and the RAC should take the lead in establishing a Data and Safety Monitoring Board for all human gene-therapy studies and that RAC members should be included in the membership of this DSMB. The DSMB would then report important findings to the RAC on a regular basis.

3. The staff that supports the RAC should also be substantially increased, so that it can contribute more effectively to high-quality research and patient safety. The RAC staff will need to coordinate the gathering, tabulation, and initial evaluation of adverse-event data for the DSMB – or contract with an existing coordinating center that regularly performs such data collection and analysis. In addition, the RAC staff could play a more active role in the design of gene-therapy protocols and the writing of better consent forms if it added staff members who could provide technical assistance to researchers and local Institutional Review Boards.

4. The Office of the Secretary for Health and Human Services should become more deeply involved in the oversight of gene-therapy research. Her office is playing an increasingly important role in all human-subjects research, as

evidenced by the move of the Office for Human Research Protections to DHHS. In addition, the Secretary can and should ensure that NIH and FDA cooperate fully in their oversight of gene-therapy research.

5. Finally, the Congress may want to consider where the RAC and its staff should be located within the Executive Branch and, more specifically, whether the RAC should be elevated to the level of DHHS. On this point I will tentatively put forward a fifth and final recommendation: Perhaps the RAC and its staff should become advisory to the Secretary of Health and Human Services (or her designee) rather than to the NIH and – less formally – to the FDA. There are three arguments that seem to me to support this proposal. First, as I noted earlier, the regulation of human-subjects research is increasingly focused in the Office of the Secretary rather than at the NIH. Second, the Office of the Secretary may be in a better position (or more willing) to support an expanded RAC staff than the NIH has been. And third, the RAC's mission differs in important ways from the roles of the NIH and the FDA. The primary role of the NIH is to fund research of excellent quality. The principal roles of the FDA vis-à-vis gene-therapy research are to regulate the research in a private and confidential manner and to approve new products. The mission that I envision for an enhanced RAC is to oversee both NIH- and privately-funded research on gene therapy, to publicly review and approve or disapprove selected gene-therapy research protocols, to monitor adverse events with the aid of a DSMB, and to keep the public informed about

new developments in the field. In my view, this expanded mission for the RAC fits most appropriately with the broad authority of the Secretary for Health and Human Services.

Mr. Chairman and Members of the Subcommittee:

The task that we are involved in today is a worthy, indeed a noble task. We are attempting to respond to system failures and the tragic death of an altruistic young man by devising a better plan for overseeing gene-therapy research in the future. If we are committed to doing this job well, I am convinced that we can create a new model for protecting the human subjects who make this research possible. If this model succeeds, public confidence in gene-therapy research will be restored, and the great promise of this important area of research will, I believe, begin to be realized. If the model succeeds, we will also have made an important contribution to the future of biomedical research. When the next major biomedical technology emerges (it may be xenotransplantation), we will be poised to oversee its development in a more effective and a more respectful manner.

Notes

United States Senate
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS
WASHINGTON, DC 20510-6300

March 6, 2000

The Honorable Donna Shalala
Secretary
Department of Health & Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Secretary Shalala,

I listened with great interest to the compelling testimony presented at the recent Senate health committee hearing on gene therapy. The witnesses described the enormous hope felt by millions of Americans that gene therapy will provide cures for a vast range of deadly diseases from AIDS to hemophilia to cancer. But the testimony of Paul Gelsinger, who spoke so movingly of the death of his son, demonstrated significant deficiencies in the current framework for gene therapy oversight. We must do all we can to see that patients who volunteer to participate in gene therapy clinical trials are protected from unnecessary risk and are fully informed of the potential side effects of the treatments they are about to receive.

I know that you are actively considering measures to improve patient safety in this area. After extensive consultation with experts in the academic world, in industry, in government and in patient advocacy organizations, I have developed a set of recommendations (attached) which I hope you will consider in weighing the possibilities for strengthening the oversight framework for gene therapy. Only by providing effective patient protection can we restore public confidence in this important area of medical research.

I commend you for taking action to improve patient protection in this important medical field, and I hope that these suggestions will be helpful. I recognize that, in addition to administrative action, legislation may be required to meet our responsibilities and restore public confidence in gene therapy oversight. I look forward to working with you and my colleagues in the Congress on any needed legislation.

With respect and appreciation,

Sincerely,

Edward M. Kennedy

the cause of the adverse events. It is equally essential that this analysis be performed by persons who have no financial stake in the outcome of the trial.

To accomplish these goals, I recommend establishing a set of Data Safety Monitoring Boards (DSMBs) to provide continuous analysis of adverse events from gene therapy clinical trials. These boards could be supported by the trial sponsor, and would be similar to the boards that are already a successful part of many clinical trials for AIDS and cancer therapies. Gene therapy DSMBs could be national in scope and could be organized so that a particular board receives reports from all gene therapy trials using a particular type of gene therapy treatment. The DSMBs would receive all adverse event reports immediately after they happen, and would determine whether the adverse event was related to the treatment given. By comparing safety data from a number of similar trials, DSMBs may discern trends in the data that might not be apparent to investigators reviewing a single trial.

Eric Kast, the young man with cystic fibrosis, gave strong testimony during the hearing about the need to protect the privacy of patients participating in trials. I recommend that the records submitted to the DSMBs be considered confidential. If careful analysis reveals a danger to patients in using a particular gene treatment, the DSMB should make a public announcement of its finding and recommend appropriate action for protecting patient safety to the FDA.

If you decide to establish DSMBs for gene therapy, I urge you to discontinue the current practice of having gene therapy investigators report adverse events separately to the Office of Biotechnology Activities at the NIH. The incidents of recent months have shown that this office is not well constituted to require and analyze hundreds of adverse event reports. Without the burden of analyzing adverse event data, the office can concentrate on its vital work of fostering public discussion of ethical guidelines for this rapidly developing field. I also recommend using the DSMBs as a conduit for adverse event reports to FDA and other appropriate federal agencies. Under this proposal, researchers would have a clearer standard for reporting adverse events. They would report all adverse events immediately to a single destination that has the expertise, resources and authority to analyze the data in a way that best protects the welfare of the patients.

Recommendations for Oversight of Gene Therapy Clinical Trials

Submission of Applications to Initiate Trials

The FDA and NIH have distinct and complementary roles in the review of applications to initiate clinical trials involving gene transfer. FDA has long been a primary guardian of patient safety in all clinical trials and has the legal authority to approve an application to begin a trial or to suspend a trial once begun. Open discussion is vital when science expands beyond its existing boundaries. NIH provides an invaluable service by allowing public comment on applications to initiate gene therapy trials that present novel ethical or scientific considerations.

The NIH should determine -- using clear published standards developed in collaboration with FDA -- which trials present such considerations, and should discuss those trials publicly at meetings of the Recombinant DNA Advisory Committee. Once this NIH committee has discussed the trial application, it should convey the results of its review to FDA. Since the Recombinant DNA Advisory Committee now concentrates on gene transfer experiments, I recommend changing its name to the Gene Transfer Advisory Committee, to reflect more accurately its current function. This committee should continue its vital work in promoting public discussion of the ethical and social implications of gene therapy.

Strengthening Oversight

The resources devoted to monitoring gene therapy trials at FDA should be commensurate with the importance of this expanding field, and I recommend upgrading the Division at FDA that provides oversight for gene therapy to a full Office. This administrative change should facilitate more vigorous oversight of the field. I also recommend directing this unit to increase significantly the number of on-site inspections it performs at sites where gene therapy trials are being conducted.

The NIH can also use its scientific expertise to increase patient safety in gene therapy. I recommend establishing a toll free hotline and an internet-based information system administered by NIH that can provide needed information to patients considering enrolling in a gene therapy clinical trial. Such a system could provide prospective volunteers with an independent source of information on the risks and benefits of participating in such trials. The NIH should also increase the training it offers to its grantees on protecting patient safety while conducting gene therapy clinical trials.

Reporting Adverse Events

Many gene therapy trials involve severely ill patients with advanced cases of deadly diseases. Sadly, many of these patients will suffer grave illness or even death during the course of a trial, whether they receive an experimental gene treatment or a standard therapy. The task of determining which adverse events are related to a gene treatment and which are caused by a patient's underlying condition is difficult, and it is essential that accounts of possible side effects be rapidly reported to a regulatory body that has the resources and technical expertise to analyze

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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NEW INITIATIVES TO PROTECT PARTICIPANTS IN GENE THERAPY TRIALS

As part of ongoing efforts to ensure patient protection in gene therapy trials, the Food and Drug Administration (FDA) and the National Institutes of Health (NIH) today announced two new initiatives to further strengthen the safeguards for individuals enrolled in clinical studies for gene therapy. These two new initiatives -- the Gene Therapy Clinical Trial Monitoring Plan and the Gene Transfer Safety Symposia -- complement and advance current patient protections.

FDA's clinical trials monitoring plan addresses emerging evidence that the monitoring by study sponsors of several recent gene therapy trials has been less than adequate. To buttress the rigor of the oversight, FDA will require that sponsors of gene therapy trials routinely submit their monitoring plans to the FDA.

FDA will review these monitoring plans and seek modifications as warranted to improve the quality of monitoring. FDA will also perform surveillance and "for cause" inspections of clinical trials to assess whether the plans are being followed and whether monitoring has been adequate to identify and correct critical problems. The sponsors will also have to address such issues as the experience and training of the monitors and the adequacy of the monitoring in their plans. In addition, NIH and FDA will seek to enhance the conduct of gene therapy trials by convening a conference of investigators at which the appropriate monitoring practices will be discussed by the most experienced professionals in the field.

Clinical trial monitoring is a powerful tool in enhancing the safety and protection of research subjects during a trial. Monitors are selected by and report to the sponsor or the sponsor's designee (e.g., a contract research organization). These monitors verify that the rights and well-being of human subjects are protected; that the conduct of the trial is in

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accordance with the protocol, regulatory requirements, and good clinical practices; and that data reporting (including safety reporting to IRB, FDA, and NIH) is accurate and complete.

In addition, in those instances where the gene therapy trial has an independent data and safety monitoring board (or equivalent) associated with it, the board's findings and recommendations regarding patient safety are shared with the IRB, FDA, and NIH. In some gene therapy trials, one or more of the investigators is also the sponsor or a member or employee of the sponsoring organization. NIH will work to develop procedures to further assure appropriately independent oversight of the conduct of such trials.

"Clinical trial monitoring and responsible reporting must be taken seriously by all parties involved in gene therapy trials," said Commissioner of Food and Drugs Jane E. Henney, M.D. "Our plan will help restore the confidence in the trials' integrity that is essential if gene therapy studies are to be able to fulfill their potential."

In a second new initiative, a series of Gene Transfer Safety Symposia, NIH and FDA will enhance patient safety by providing critical forums for the sharing and analysis of medical and scientific data from gene transfer research.

The symposia, which are expected to take place about four times a year, will bring together leading experts in gene transfer research and give them an opportunity to publicly discuss medical and scientific data germane to their specialties.

The first symposium will take place during this week's meeting of the Recombinant DNA Advisory Committee (RAC). Scientists and physicians will discuss the safety and future clinical applications of a new class of adenoviral vectors that have been extensively altered with the aim of improved safety.

Subsequent symposia will be held at the RAC, FDA's Biological Response Modifier Advisory Committee, and other venues. These symposia will address such gene transfer topics as monitoring of data safety; cardiovascular complications of vector administration; good clinical practice in research; cell and gene therapy guidance development for product quality control and assurance; entry criteria and informed consent for participants in gene transfer research; and use of drugs to control promoters in gene therapy vectors. Future symposia also will focus on topics such as the use of a particular vector, a specific disease for which gene transfer is an experimental therapeutic approach

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(such as hemophilia, Alzheimer's disease, or sickle cell disease) and/or a specific population of patients enrolled in gene transfer studies, such as newborns, children, the elderly, or normal volunteers.

To further increase their educational outreach efforts, FDA and NIH also will provide support for professional organizations and academic centers interested in holding safety conferences focused on gene therapy.

"The knowledge and understanding gained through these safety symposia and educational outreach efforts will guide the conduct of current trials and enhance the design of future gene transfer trials to maximize patient safety," said NIH Acting Director Ruth Kirschstein.

FDA also announced today that it is notifying all sponsors of gene therapy trials to supply additional information about cell banks, viral banks and other gene therapy products produced or generated in their facilities for potential use in non-clinical or clinical studies of human gene therapy. Among other gene therapy related information, FDA is asking the sponsors to provide quality control information for each lot of products produced in their facilities or used in their clinical trials.

Today's initiatives are part of the Administration's ongoing efforts to ensure the safety of patients enrolled in gene therapy clinical trials. Last month, President Clinton asked Health and Human Services Secretary Donna E. Shalala to instruct FDA and NIH to accelerate their review of gene therapy guidelines and regulations. Specifically, the President asked how information can be better shared with the public and whether requirements on informed consent need to be strengthened.

In the past few months, FDA and NIH have taken individual and cooperative actions to achieve greater adherence by researchers to existing requirements and guidance and to bolster the protection of study participants and the integrity of gene therapy trials. These include:

- The NIH will undertake a series of "not for cause" site visits to NIH-funded institutions to review institutional understanding of, and compliance with, a range of NIH rules, regulations, and guidelines, including the *NIH Guidelines* and policies relevant to gene transfer research, conflict of interest, and invention reporting.

- NIH directed all institutions conducting human gene transfer research to review their institutional policies and

procedures to ensure compliance with the NIH Guidelines. NIH is also contacting every clinical gene transfer investigator to ensure that they have submitted all serious adverse events to the NIH, including serious adverse events from trials that are no longer active.

- A working group reporting to the NIH Director was established to comprehensively review in public session the role of the NIH in gene therapy clinical trial oversight.
- A subcommittee of the RAC is examining the reporting, analysis and public disclosure of serious adverse events to the NIH, with the aim of recommending changes in the *NIH Guidelines*.
- FDA will conduct more inspections to increase oversight of Investigational New Drug applications in gene therapy.
- NIH is completing the development of an interactive web-based database to provide public access to data on gene transfer research, which will be online by October 2000.
- FDA plans to issue a proposed rule on the public disclosure of information regarding gene therapy clinical trials that would provide more information on these trials to the general public.
- FDA is enhancing regulatory research to improve product safety.
- FDA has provided guidance documents to industry and other interested parties on gene therapy products and will take action to build upon existing guidance.

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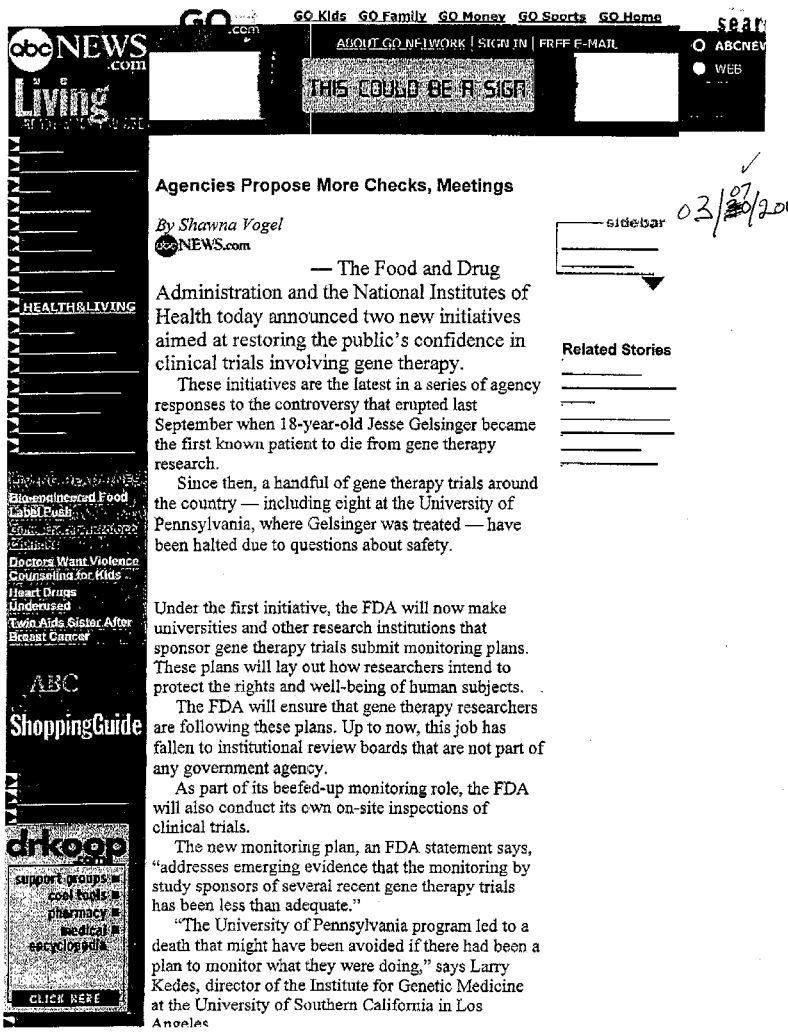

Agencies Propose More Checks, Meetings

By Shawna Vogel
ABCNEWS.com

— The Food and Drug Administration and the National Institutes of Health today announced two new initiatives aimed at restoring the public's confidence in clinical trials involving gene therapy.

These initiatives are the latest in a series of agency responses to the controversy that erupted last September when 18-year-old Jesse Gelsinger became the first known patient to die from gene therapy research.

Since then, a handful of gene therapy trials around the country — including eight at the University of Pennsylvania, where Gelsinger was treated — have been halted due to questions about safety.

Under the first initiative, the FDA will now make universities and other research institutions that sponsor gene therapy trials submit monitoring plans. These plans will lay out how researchers intend to protect the rights and well-being of human subjects.

The FDA will ensure that gene therapy researchers are following these plans. Up to now, this job has fallen to institutional review boards that are not part of any government agency.

As part of its beefed-up monitoring role, the FDA will also conduct its own on-site inspections of clinical trials.

The new monitoring plan, an FDA statement says, "addresses emerging evidence that the monitoring by study sponsors of several recent gene therapy trials has been less than adequate."

"The University of Pennsylvania program led to a death that might have been avoided if there had been a plan to monitor what they were doing," says Larry Kedes, director of the Institute for Genetic Medicine at the University of Southern California in Los Angeles

sidebar

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While Kedes says physicians are generally well-meaning, the nature of the research requires them to take risks, so it is reasonable for an external agency to monitor how the research gets done.

In a second initiative, the NIH and the FDA will also host a series of meetings in which scientists can share the insights they have gathered from doing gene therapy trials.

The aim of these meetings is to bring the most up-to-date scientific knowledge to bear on the safety of patients in ongoing as well as future trials. The first such meeting will take place during this week's meeting of the Recombinant DNA Advisory Committee.

Gene therapy can be defined as the introduction of nucleic acids, usually DNA or genes, into cells to prevent or reverse a pathologic process. While hundreds of protocols have been tried and thousands of patients treated, very little true success has yet to been achieved. However, gene therapy is a young field. It will take time before its true potential is realized.

Clinicians originally conceived gene therapy as a means to treat genetic disorders characterized by single altered or missing proteins responsible for the disease. They would introduce a normal copy of a gene into cells to restore the function of the absent or distorted gene. But other applications allowed researchers to express genes that supply a therapeutic function, such as decreasing artery wall thickness in coronary artery disease or delivering lethal toxins to cancer cells.

Clearly, different diseases require different approaches. One of the major obstacles in gene therapy is delivering therapeutic levels of genes to the appropriate tissue. To do this, gene therapists have developed two ways to get the genes into cells: One takes advantage of the ability of viruses to get their genes into cells. The other relies on chemical synthesis of gene-delivery systems.

Viruses have evolved over millions of years to be efficient carriers of genetic materials into cells. These genes normally code for the proteins that take over the cells and make us ill. To make viral vectors, or gene delivery systems, most of the genetic material from the virus is removed. This weakens the virus's ability to cause disease and makes room for the insertion of therapeutic genes. To make a viral gene delivery unit, scientists take the genetically modified DNA with the therapeutic gene and put into the viral coat manufactured in the laboratory. The particles are purified and then added to cells or injected into the body.

The second method is non-viral, in which the DNA is encapsulated into artificial material.

Getting the genes in question to the tissue can occur inside and outside the body. In the external approach,

cells, such as bone marrow cells, are removed, genetically modified and transplanted back into the body. Other gene transfer involves the infusion of a vehicle that carries the DNA into the appropriate cells to achieve the desired effect. Ultimately, we would like to be able to take our dose of DNA orally or by single injection.

Like any technology, it is likely today's vectors and approaches will be replaced by better strategies. Areas of intense research include designing vectors that will target specific tissues, technologies that allow for regulated gene expression, and better animal models that mimic human diseases for pre-clinical testing.

— Mark Kay is on the ABCNEWS Medical Advisory Board and is director of the human gene therapy program at Stanford University's medical school.

Mr. MCCARTHY. And I would like to modify even that a little. Since I submitted my testimony I have spent some time in the library and found references to a number of other sources that make recommendations identical to, or similar to the ones that I'm making today. So I will add those, if I may submit those as well.

Mr. MICA. Without objection, and within in the time limits that have been announced. Go ahead.

Mr. MCCARTHY. As has been noted earlier in the hearing, Institutional Review Boards were initiated by the Public Health Service in 1966. It's not so well-known that in the late 1960's, and I can't give you a specific year, the National Heart Institute, now National Heart, Lung and Blood Institute, at NIH created an additional kind of oversight body to look at large multi-centered trials, and to collect and analyze data, particularly adverse event data, in those trials. Data and Safety Monitoring Boards, while nowhere near as well-known as IRBs, are indeed almost as old and as honorable as the IRBs.

During the seventies Dr. Robert Gordon, who was for a time the Director of the Clinical Center at NIH, and Dr. Curtis Meinert, from Johns Hopkins University, spent a great deal of time refining and defining the work of Data and Safety Monitoring Boards. As the funding patterns for NIH grants changed from grants that were made to a single investigator at a single institution to multicentered trials where there might be anywhere from 5 to 50 or even 100 different centers, each with itw own investigation carrying out the same protocol. The Data and Safety Monitoring Board has become the instrument most sensitive to being able to receive and process adverse event data and other information about multicentered trials from many sources; evaluate those data and other information with the help of professional statisticians and thus to get an overview of the trial that is literally impossible to get at any single center or any single institution. We are faced with something of an anomaly. The Data and Safety Monitoring Boards are not established by regulation and exist in less than half of the multi-centered trials that are conducted in this country. They are the bodies that have the best information and carry out the most careful analysis of the data. On the other hand, IRBs are the committees who, according to regulation, have the responsibility of determining whether trials should be stopped, modified or continued. Consequently the most complete knowledge is in one committee, and decisionmaking responsibility is in another committee. It seems to me that we can make a very constructive kind of change in the regulations so that the Data and Safety Monitoring Boards communicate their findings back to the IRBs. If that step is taken, it will, first take some work off the IRBs and begin to address the workload problem identified in the Inspector General's report, and second, it will improve the quality of the information on which the IRB makes its decision to continue, modify or discontinue research projects.

All of the kinds of incidents you've addressed today in your hearing seem to me to indicate that now is the time to start afresh. Modify the regulations so that the data held by Data and Safety Monitoring Boards is made available to the IRBs, so that the best

possible decisions concerning the continuation and oversight of trials can be made.

Typically, as we heard testified earlier from the Inspector General, the IRBs receive adverse event data, but it is raw data. IRBs don't know which arm of the study the adverse event occurred on. They don't know whether it was in an elderly subject or a young subject. They don't know which adverse events result from complications of disease of the subject. They cannot tell whether the adverse event was caused by the research, by the underlying disease condition, or by some inherent condition that pertains to the subject himself or herself.

Data and Safety Monitoring Boards display the data in a number of different ways: according to age; gender; race; ethnicity and a whole variety of other categories so that they can evaluate adverse events; tell which ones are very serious; which ones are likely to be associated with the research intervention; and which ones might have occurred anyway because of underlying disease conditions. DSMBs are able to give the kind of analysis that will refine the judgments about the safety of the research, and whether it should continue.

So my recommendation to you and to the rest of the committee today is simply that one of the ways the Inspector General's report could be used or could be capitalized upon would be simply to adjust the regulations and by putting some kind of a regulatory link requiring Data and Safety Monitoring Boards under certain conditions and, second, making sure that the data that they gather and analyze is carefully and thoroughly shared with the IRBs so the IRBs then can—with less work and with greater accuracy—meet the responsibilities that are assigned to them. This will not, in my judgment, decrease costs because the Data and Safety Monitoring Boards have full-time statisticians working for them. They have costly experts.

I participated in a Data and Safety Monitoring Board meeting yesterday. There was an expert from Germany, one from England, three from the United States and myself. Obviously to have a meeting of that kind is very costly. Statisticians generated—relative to on one study—about 300 pages of data. The DSMB spent the best part of the day evaluating that data to determine whether the study should go on. That's a very costly process, but I can assure you that the subjects in that study received the very best safety efforts that are humanly possible.

No one can guarantee that mistakes will not be made, but I think when the data is processed in such a thorough way, the chances of a mistake become exceedingly small. That's what we owe to our research subjects. Even though oversight costs may be raised. On the other hand, the cost to the local IRBs will be reduced because their workload of analyzing large quantities of adverse data will already be done for them by statistical experts. They will be able to make much more enlightened decisions as to the research in their institution.

I will be glad, Mr. Chairman, to answer any questions that you may have concerning this issue or any others.

Mr. MICA. Thank you, and what we'll do is suspend questioning until we've heard from our final witness. He's also very patient. Dr.

Robert Amdur, and he is the associate professor, associate chair of clinical affairs, Department of Radiology and Oncology at the University of Florida. Welcome, and you're recognized, sir.

Dr. AMDUR. Thank you. Good afternoon, Mr. Chairman, and other committee members.

As you mentioned, my name is Robert Amdur. I am a physician at the University of Florida. My qualifications to speak to you today about the protection of human research subjects are that I am a medical researcher who frequently enrolls patients in research studies. For the past 10 years I have played a leadership role in defining and implementing ethical standards for research through my participation in the Institutional Review Board and related national organizations.

I am here today representing a national nonprofit organization called PRIM&R, which stands for Public Responsibility in Medicine and Research. For over 25 years, the primary mission of PRIM&R has been to bring researchers, ethicists, and research regulators together to improve our system for protecting the rights and welfare of human research subjects.

Since 1974, PRIM&R has sponsored over 100 educational conferences, published hundreds of documents, set up onsite workshops for institutions with special needs, and many other important activities that meaningfully improve the way research is done in this country.

I have submitted a written statement which goes into detail about the challenges that currently stress our system of protecting human research subjects, and PRIM&R's plans for helping the research community respond to these challenges.

At this time I would like to formally request that a written copy of my testimony be included for the Record.

Mr. MICA. Without objection, so ordered.

[The prepared statement of Dr. Amdur follows:]

PRIM&R Public Responsibility in Medicine and Research

Statement of
Public Responsibility in Medicine and Research (PRIM&R)
on
The Protection of Human Subjects Involved in Research

Presented to the
Subcommittee on Criminal Justice,
Drug Policy and Human Resources
of the
Committee on Government Reform
United States House of Representatives

Presented by
Robert Amdur, M.D.
Associate Professor
Associate Chair, Clinical Affairs
Department of Radiology and Oncology
University of Florida

May 3, 2000

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Recommendations for Improving the Protection of Human Research Subjects

Good morning Representative Mica, Honorable Committee members, and other Congressional staff personnel. I am Dr. Robert Amdur, Associate Professor and Associate Chair in the Department of Radiology and Oncology at the University of Florida. Until last summer, I was a faculty member in the Department of Radiology and Oncology at Dartmouth Medical School, where I also chaired the institutional review board, hereinafter referred to as the "IRB."

I am here today representing Public Responsibility in Medicine and Research (PRIM&R), a non-profit organization based in Boston. PRIM&R just celebrated its twenty-fifth anniversary, but was in existence for a few years prior to its actual incorporation. Throughout its existence, PRIM&R has been committed to the advancement of science, and to the consistent application of ethical precepts in both medicine and research. PRIM&R brings the research and IRB communities together to address emerging issues and current problems via between three and four conferences per year. These conferences have been repeatedly cited as the most useful educational vehicle currently available for those in the research review field. Our "sister" organization, Applied Research Ethics National Association, (ARENA), is a membership organization for those involved in the day to day application of ethical principles, governmental regulations, and other policies regarding biomedical, behavioral, and basic research.

Since 1974, PRIM&R has sponsored over 100 such conferences, published almost as many volumes which document the proceedings of those meetings, sent educators into dozens of institutions, and served as the "source for all things relating to IRBs" in this country. It has been a privilege for PRIM&R to work with the IRB community, and we have consistently found its members to be dedicated, hard-working, principled, and committed to our shared goal of advancing responsible research and protecting those who participate therein. We have also consistently found most of those who administer and chair IRBs to be lacking the proper support, and thus chronically understaffed and overworked.

Thank you for the opportunity to share with you PRIM&R's "wish list" for the IRB community. In the interest of time, I have included only three priority items, but our staff and Board of Directors, headed by Dr. Sanford Chodosh, would be pleased to expand and amplify this list upon request.

First, PRIM&R considers it imperative that the Common Rule, which mandates certain protections for federally funded research, be extended to **all** research, irrespective of funding source. There are no ethically permissible grounds upon which continuation of this discriminatory practice can comfortably rest, and we thus urge that Congress act quickly to extend the threshold protections afforded by regulation to **everyone** who participates in research as a human subject. PRIM&R maintains that all who participate in research are potentially vulnerable, given the disparate power relationship between scientist and subject. To permit private funders of research to proceed without the same ethical imperatives and other safeguards required for federally funded studies is unsupportable, and we hope, soon to be an anachronism.

Secondly, there are presently two central sets of regulations and policies under which IRBs operate, those promulgated by the Office for Protection from Research Risks of the National Institutes of Health, and those promulgated by the FDA. Although similar in many respects, these regulatory procedures are not identical, and this lack of congruence is yet another yoke that is unnecessarily heavy for IRBs to bear. Were Congress to direct these two Agencies to fuse, or at least better coordinate, the implementation of their respective sets of regulations, IRBs would be less burdened, and thus better able to perform those tasks which more directly impact the protection of human subjects.

Thirdly, we feel strongly, and have taken steps to "operationalize" the belief, that a voluntary accreditation system based on carefully wrought performance standards would go a long way toward giving research institutions the educational tools and constructive incentives they need to better perform the subject protection portion of their jobs. Toward that end, PRIM&R has launched an affiliated not-for-profit corporation called the "Association for the Accreditation of Human Research Protection Programs," otherwise known as AAHRPP. AAHRPP seeks to provide "a process of voluntary peer review and education among entities concerned with research involving humans, in order to promote preservation of the rights and welfare of subjects in research, and to promote compliance with applicable ethical and regulatory standards."

While the concept of accreditation has been on PRIM&R's "to do" list for some years, it became an action item only eighteen months ago. Since AAHRPP's inception, it has drawn strong support from the community of research institutions, both hospitals and universities alike. This ready acceptance reflects a recognition of the relative educational vacuum that now exists, and AAHRPP's potential to fill it. More specifically, the overwhelmingly positive response of the research and IRB communities to accreditation in general, and to AAHRPP in particular, also confirms our long held assumption that institutions want, like most of us, to do the right thing, but sometimes don't know what "the right thing" is. The AAHRPP accreditation process will be collegial, collaborative, highly customized, committed to continuing quality improvement, rather than an "inspection" in the traditional sense, and, above all, highly educational.

In order to achieve these ends, AAHRPP has empanelled sixteen senior IRB chairs, administrators, researchers, bioethicists, federal representatives, and industry personnel to develop a set of performance standards which will encourage research programs to adopt the "best practices" in their respective areas. While indispensable as a threshold level of protection for those who participate in research, existing Federal regulations are not easily convertible to the kinds of "best practices," or "critical standards," which help explain **why** an IRB or a researcher should operate in a certain way, and not just **how** they should operate.

As has been the case with many past PRIM&R initiatives, we plan to involve a number of major stakeholding organizations in this new accreditation enterprise; foremost among them, the Association of American Medical Colleges, with whom we have successfully partnered on a number of projects of shared interest. The AAMC represents all 125 accredited U.S. medical schools, over 400 teaching hospitals, and 89 scientific and academic societies. Its member institutions conduct the majority of clinical research in this country, and the safety of those who volunteer to participate as research subjects is thus a significant concern of that organization, as well as of PRIM&R's. The AAMC has been in extensive dialogue with the PRIM&R board, and more recently with members of the AAHRPP board. The AAMC is extremely interested in the creation of a not-for-profit organizational structure that would help ensure the success of this accreditation initiative. The AAMC has expressed its firm endorsement of this initiative, and hopes to see AAHRPP structured in a way that will promote its success. PRIM&R and AAHRPP are, in turn, grateful for AAMC's support, and confident that other stakeholders will share their view and similarly support this effort.

How will AAHRPP's accreditation system work? Each research institution, be it a hospital, university, pharmaceutical house, biotech facility, or freestanding clinic, etc., which applies for AAHRPP accreditation will receive a copy of the above-described performance standards. Two assessments will follow: First, a self-assessment by the program itself will take place, and a peer review site visit will then follow. The former assessment will consist of a survey-type instrument, which must be completed by the relevant departments of the institution, i.e., institutional officials, IRB administrators, members, chair(s), and a representative sampling of researchers and principal investigators.

This self-assessment will be followed by a site visit of between one and two days for the average IRB, and will involve between two and three site visitors. PRIM&R has already obtained commitments from the most senior and respected IRB and research ethics representatives in the country to serve as AAHRPP site visitors, and the protocols pursuant to which these assessments will be conducted are constructive, proactive, and highly interactive. In short, we have no doubt that AAHRPP site visitors will be welcomed – nay wanted – because the informational exchange will be enormously beneficial to each prospective "accreditee." Following each such encounter, the site visitors will draft both a report and a set of recommendations outlining the resources and enhancements needed in order for the research protection program under examination to optimally perform its functions.

It is our ardent belief that the performance standards and "best practices" AAHRPP is developing, when combined with on-site reviews which focus on education, will encourage research institutions to achieve a high level of performance which goes beyond the minimal adherence to federal requirements. The performance standards will provide guidance to institutions that seek to meet contemporary standards of research ethics and federal oversight, thereby bringing a much-needed yardstick to a complex and high stakes area. Although this process is still in its infancy, we have every reason to expect that it will go a long way toward closing the knowledge – and consequent "protection" - gap that now exists among IRBs. When an institution seeks and obtains AAHRPP accreditation, a program of continuous quality improvement will be fostered and will, we maintain, positively impact the experience of those who participate in research as human subjects.

In this manner, PRIM&R has fashioned a solution which we are persuaded will bear fruit, and we therefore urge your strong support thereof. Research institutions must assure all four parties to the process, i.e. subjects, researchers, sponsors, and regulators, that the environment in which research is conducted "walks the walk and talks the talk" when it comes to protecting human research subjects. There is much talk today of "partnering" with the research participants, of attempting to more sensitively consider their needs and interests, and of ways in which the recruitment, consent, and monitoring processes can all be improved. These noble ends can best be accomplished by establishing a strong and well functioning IRB system. This, in turn, requires an acknowledgment of the commonality of interest among the four parties mentioned above, as well as the financial resources to – as Garrison Keilor would say – "do what you got to do" to get the job done with care and commitment.

It costs a lot of money to run a respected human subjects protection program and the IRB that attends it, and many institutions are presently unwilling to expend the funds needed to accomplish this goal. Unfortunately, IRBs don't bring money into the institution in the traditional sense, and they are thus given short shrift by many institutional officials in the allocations process. But because IRBs are the gatekeepers between irresponsible, or misguided, research, and those who are being asked to participate therein, adequate funding is essential to the effective discharge of their duties. You know the dilemma well… if you don't have the wherewithal to do your job, you cannot do it "right." So, too, with IRBs. They cannot fulfill their assigned protective function without the financial support and staffing appropriate to the loads they are being asked to carry, **and** without the backdrop of an institutional culture which elevates ethics to its proper and lofty level. The result of underfunded, and otherwise unsupported, programs can be seen from the rash of recent "shutdowns," and the knowledge that for each shutdown, there are many programs thinking "there but for the grace of God, go I."

Why accreditation? We believe that accreditation is an intervention likely to succeed, as it is voluntary, educationally driven, and peer mediated. Having Congressional endorsement of AAHRPP's efforts would be an early boost, and one whose impact could not be underestimated. Each of you would like to see the system for protecting human subjects strengthened, and so would we. When one considers the many, less likely, professions and enterprises which are accredited, e.g., sanitation workers, medical records librarians, undertakers, arborists, barbers, cameramen, organic farmers, and mechanics, one begins to instead ask "why **not** accreditation?" The need to establish formal standards, and the concurrent need to identify a way to recognize when programs and professionals in a given field are meeting those standards, is obvious, and, long overdue, we feel in the area of human subjects

protection. This is a complex, and, as seen in the recent case of Jesse Gelsinger, very high stakes arena, deserving of this fresh approach.

What happens when professionals do not adhere to the ethical standards that they hold in common? In answering that question, it is noteworthy that much of the impetus for current day research ethics stems from the Nazi atrocities and our shared vow of "never again." Yesterday was Holocaust Remembrance Day, and in one service commemorating the horrors of the Third Reich, Eli Wiesel, Nobel Laureate, author, teacher, and survivor of the camps, said, "without its ethical dimension, civilization is vulnerable." Many human subjects are vulnerable, many IRBs want to do a better job of helping them, and we all turn to you for relief and guidance.

In closing, I want to end where I began, stating that those who staff, sit on, and chair IRBs are largely principled, and unequivocally dedicated to protecting human subjects. As you search for solutions, please work hard to ensure that principles and practicalities do not collide. Any new initiatives should be aimed at adding value to the protection process **without** adding unreasonable and unproductive hurdles for the IRB. This is an achievable objective, and PRIM&R looks forward to continuing its work to help make it a reality.

Thank you for your consideration of these remarks. Our final, and most heartfelt, thanks go to the legions of research subjects who volunteer to participate in research. They are the heroes of this story, and it is our challenge and obligation to honor – and protect -- them as such.

Appendix A

What is PRIM&R?

Public Responsibility in Medicine and Research (PRIM&R), a national nonprofit organization founded in 1974, is a strong advocate for ethical human and animal research. By holding four nationwide conferences each year and publishing reports, PRIM&R is committed to the advancement of strong research programs and the consistent application of ethical precepts in both medicine and research. The conferences, hosted in Boston and other U.S. cities, provide an educational forum for the analysis of various biomedical and bioethical issues.

PRIM&R's conference participants come from throughout the United States, Canada, and Europe and include: Institutional Review Board (IRB) and Institutional Animal Care and Use Committee (IACUC) members and administrators, biomedical researchers, physicians, nurses, hospital administrators and other health care personnel, healthcare ethics committee members, lawyers, governmental representatives, members of the academic community, patient and animal welfare advocates, and journalists.

PRIM&R's annual IRB and IACUC conferences provide education and orientation to IRB and IACUC members and to those who deal primarily with behavioral science research with humans. PRIM&R also offers on-site training programs for those institutions that would like a more customized educational program.

PRIM&R also provides references and referrals, distributes articles and educational materials, and answers questions. Conference related educational materials and special reports are available for purchase. While not a lobbying organization, PRIM&R has coordinated information for testimony before legislative committees and other hearings.

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Appendix B

Addendum to Testimony Contained Above:

There are three other items which, in the interest of time we are not able to discuss today, but which, PRIM&R feels, are indispensable to any efforts to redress current deficiencies in the system of protecting human subjects. These are issues with which research directors, IRB members, and regulatory officials are currently struggling in an effort to protect the rights and welfare of research participants without inhibiting the conduct of meaningful research. I share these with you in hopes of identifying additional areas that are ripe for future review and possible guidance.

1. Distinguishing research from non-research activities

Laws, regulations, and ethical codes often have different standards for *research* and non-research activities. The problem with discussing ethical standards in terms of a *research* versus non-research model is that it is difficult to make this distinction for many of the activities that are now part of the fabric of our modern healthcare system. Does modification of a standard surgical technique or use of a medication in a way that has not been approved by the Food and Drug Administration constitute *research* or innovative medical practice? Should retrospective medical record review by a qualified physician be classified as *research* or a non-research outcome analysis? Is an analysis of the association between a hospital's nurse staffing model and the length of hospital stay following a given surgical procedure *Health Services Research* or Quality Assessment?

To those not familiar with healthcare regulation the above questions may seem like an academic exercise about semantics. However, to IRB directors, federal research regulators, medical center compliance officers and other people who make important decisions based on research-specific standards, the ability to identify research intent with the large volume of diverse projects that are part of the modern healthcare system is serious business. In order to properly administer a system of protection of research subjects it is essential that we establish unambiguous criteria for classifying a

project as *research* from the regulatory standpoint. Several members of the IRB community are currently working on a decision algorithm to more concretely address this issue.

2. Evaluating the quality of informed consent

A major problem with the current system of research regulation as it relates to ethical standards is that it does not require evaluation of important endpoints of ethical behavior. Federal regulations currently require documentation of a process that is likely to promote ethical standards but there is little in the current process that directs the IRB, or some other group, to document that such standards were met. For example, a major focus of current federal regulations, and most IRB reviews, is the wording of the consent document (ref). The regulatory system spends and enormous amount of resources being sure that researchers give potential participants a piece of paper that contains the information that they need to make an informed decision about research participation.

The problem with this approach is that it does nothing to evaluate the critical ethical issue- namely, do subjects understand the essential elements of informed consent and are they making the decision to participate in research voluntarily without coercion? Based on recent newspaper stories and empirical studies of knowledge and motivation in research participants it is clear that it is not unusual for subjects to be enrolled in high-risk research without adequate informed consent.

As informed consent is the backbone of ethical research it is essential that our system of protection of research subjects include a focused effort to evaluate the quality, and conditions, of informed consent in subjects who have agreed to participate in research studies. A meaningful quality assessment effort of this kind must be ongoing and will require substantial resources in terms of personnel and training. At present, a system for evaluating the quality of informed consent has not been standardized, but several institutions are doing pilot work in this area.

3. Conflict of Interest of research institutions and investigators

A sensitive subject at research institutions is the role that financial incentives play in the design and conduct of clinical research trials. Industry sponsors have a strong incentive to design trials that produce a positive result rather than test a new product against best known therapy. Research investigators often depend on the per-capita profit from enrolling subjects in research studies to fund activities that are important for their professional development. Medical schools increasingly rely on profits from industry-sponsored research to fund core academic programs.

From the ethical standpoint the question is not if conflicts of interest exist but if they can be managed so that they do not lead to unacceptable bias on the part of research directors or a feeling of deception on the part of research subjects. Currently the IRB system does little to evaluate and correct problems related to conflict of interest.

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Dr. AMDUR. In the next few minutes, I would like to emphasize three requests that I hope you will focus on as you decide on new Federal initiatives related to research protections.

Request No. 1 is to pass Federal legislation that requires that all research in the United States comply with the same high level of ethical standards, regardless of funding source. The ethicality standards that should be met when conducting research on human subjects are described in the Department of Health and Human Services regulations that are often referred to as the Common Rule.

A problem with our current situation is that the authority of the Common Rule does not extend to some situations where research is sponsored by private industry. It makes no sense to have different ethical standards for research depending on funding source. All Americans should be afforded the same high level of protection and oversight. Medical progress will not be compromised by a more comprehensive regulatory structure, and PRIM&R urges you to support legislation that eliminates the two-class system of research protection that we currently have in this country.

Request No. 2 is to pass legislation that consolidates the multiple different sets of Federal research regulations that currently exist into a single regulatory reference. The Department of Health and Human Services currently has one set of regulations, the FDA has another, the Department of Education has its own rules, and so on. In many cases, the regulations from these different Federal agencies are congruent, but in other situations they are not. In still others it is unclear what they are.

As a result, researchers, industrial sponsors, IRB members, institutional officials, spend a tremendous amount of time and energy trying to figure out what hoops to jump through when different Federal agencies are involved, as is the common situation in both industry-sponsored and federally funded research studies.

The situation is ridiculous. There is no reason that we should not have a single set of regulations that applies to all research involving human subjects, regardless of the Federal agency that is involved or the funding source.

Request No. 3 is to ask you to support PRIM&R's efforts to create a formal program for accrediting each institution's system for protecting human research subjects. Protecting human subjects requires much more than an accounting type of checklist or audit of IRB paperwork. It requires onsite evaluation by trained professionals of objective and subjective end points, such as the level of institutional support for the IRB, the knowledge of research investigators about ethical standards, the commitment of institutional officials to shielding research regulators from financial conflicts of interest and other pressures, and eventually, to documenting objective end points of ethical behavior, such as the quality of informed consent for the subjects that have been enrolled in research studies.

To set up a system for accrediting an institutional program for protecting research subjects, PRIM&R has recently formed an affiliated not-for-profit corporation called the Association for the Accreditation of Human Research Protection Programs. The acronym for it is AAHRPP. The current plan is to make the AAHRPP ac-

creditation program voluntary, and we believe that most institutions will actively seek AAHRPP accreditation as a way of increasing the integrity of their research programs.

Time does not permit me to describe the details of the AAHRPP accreditation process. This information is provided in my written statement. I am happy to explain anything related to this in the question session.

I would like to conclude my remarks by reminding you that this is not about a bunch of paperwork that enhances the power or budget of some Federal agency or a special interest group. Modern society is stuck between a rock and a hard place. We must conduct complex and often dangerous research with human subjects if we are to improve the condition of life on this planet.

There is often a tension between the ethical standards that we need to work within and a scientific agenda. We can create an environment where we promote meaningful research in a way that does not exploit in any way the rights and welfare of research subjects, but we need the strong arm of the Federal Government to make this happen and we need Federal support to be applied correctly.

Our current IRB system is a good one. It is a result of the Nuremberg War Crimes Trial that exposed the shameful, unethical research that was conducted by Nazi physicians in the name of medical science during World War II. Earlier this week, the world observed Holocaust Remembrance Day in honor of those who suffered during the awful period in human history.

In one remembrance ceremony, the Nobel Laureate Elie Wiesel said, "Without its ethical dimension, civilization is vulnerable." PRIM&R and many other members of the research community hope you will act swiftly and decisively to improve the system of protecting human research subjects in this country. The AAHRPP accreditation program and the other changes that I have mentioned are steps in the right direction.

On behalf of PRIM&R, thank you for inviting me. I am happy to provide any other information that would be useful. Thank you.

Mr. MICA. Thank you and each of our witnesses on this panel for your testimony. I apologize, again, for the delay in the hearing, but we had floor votes and then we had the required participation in the committee hearing.

Again, I would like to proceed with some questions, first maybe to Mr. Curtin. Well, you have all basically criticized some of the current functioning, operation, of the IRBs. Mr. McCarthy did not get into too much of that, he spoke mostly of the DSMBs. But the current system appears to be somewhat flawed.

I guess if we started out maybe with informed consent, do you think it might be possible to have a basic standard informed consent procedure that would be good for all human research testing, Mr. Curtin?

Mr. CURTIN. That seems very bureaucratic to me, very inflexible. I would hope that we would be able to rely upon individual researchers and IRBs to come up with—to develop—the informed consent that most fits the research project that they are looking at.

Maybe that is too theoretical, maybe it cannot be done.

Mr. MICA. I don't know if your daughter was afforded informed consent. Was she?

Mr. CURTIN. Absolutely not.

Mr. MICA. Absolutely not. So first of all, there was not any in place?

Mr. CURTIN. Not for her. Well, if she answered it, obviously, but for other family members, no.

Mr. MICA. For her, for herself, she did have informed consent?

Mr. CURTIN. Yes.

Mr. MICA. Were you satisfied with that? Your protest then goes beyond her situation and her giving informed consent. I understand your concern about your privacy, her disclosure of your medical record. But were you satisfied with the informed consent that she was provided?

Mr. CURTIN. The informed consent really was if she responded to it, that would be considered the informed consent. She would have voluntarily participated if she had filled out the questionnaire and put it in a return envelope and sent it in.

Mr. MICA. To step back first, does everybody believe that there should be a requirement for informed consent?

Mr. CURTIN. I think there should have been a statement in the instructions saying, if you are going to answer for your other family members, you might want to tell them that you are doing that.

Mr. MICA. We have not gotten to family yet. We are talking about an individual who is going to participate or someone who is a guardian or legally responsible for that individual. There should be informed consent.

Everybody agrees on that?

Dr. AMDUR. There are situations where it is appropriate and necessary to conduct research without informed consent, and those situations are described and provided for in current HHS regulations.

A typical example would be emergency situations where it is not possible to get it, to conduct research with there being informed consent. There are other situations such as health services research involving access to medical records where risk is minimal and it is not possible or practicable to conduct research with a requirement for informed consent.

The fundamental ethical standards that we use when we think about these and analyze them and say what is appropriate, what is not, what rights and welfares are important to maintain, need not be violated in certain circumstances without getting informed consent.

Mr. MICA. Dr. Amdur, you are the one I thought that had come forward in past Federal law or regulations and set standards. That is what I am trying to get at.

I had, sitting where Mr. McCarthy is, the representative of HHS. He said they had all the authority they needed to deal with these situations. It sounded like he did not have any recommendations for legislative changes.

You have come forward and recommended something. Maybe you could elaborate on what you envision we should be doing as a Federal Government to again provide that there is adequate informed consent in human patient testing, that there is not a problem with the operation of an IRB.

Right now, they cannot even tell me how many IRBs there are, OK? And then the operation of an IRB, should we be more involved

in a conflict of interest, making certain there are not conflicts of interest?

You heard this explosion and expansion of human research in just the whole biotech industry. All of the breakthroughs in medicine, testing, have just dramatically exploded. We hear something new every day.

We as government do not want to stand in the way of research, but you have some basic protections that should be in place. Now, HHS said that they have adequate authority. You are saying that we should have some Federal regulations or laws and set some standards. Maybe you can elaborate.

Dr. AMDUR. You have raised a number of points. To go into detail about each one I think would be beyond the scope of this discussion, conflict of interest, etc.

My response would be that the requests that I listed were specific regulatory changes that will make this current system work better.

Mr. MICA. The HHS has the ability to institute regulations, so it is not a matter of changing the law, or is it? Are you aware of where we need to change the law?

Dr. AMDUR. Perhaps I am mistaken in terms of exactly who initiates the law. Really, though, I think.

Mr. MICA. We initiate the law. What we do is when they have the need to be changed from time to time, we defer to HHS and the agencies to institute regulations.

Dr. AMDUR. I don't know any delicate way to say this. The point is, HHS could have made these changes, should have made these changes. PRIM&R sponsors two national meetings a year. The IRB world knows many changes that need to be made to make the system work better, which is a good system. They have not been made because of Federal bureaucratic inertia, turf wars, whatever. That is the reason that I am saying to you, I don't know what the problem is.

Mr. MICA. I was trying to see if you had a recommendation in a legislative context. Most of it appears to be regulatory in nature. The failure of HHS to institute even the recommendations your group has made, we have the same problem. We had the IG sitting next to HHS and telling us that even basic things that were recommended back in 1998 still have not been instituted.

We are looking first at the statutory and the larger picture, our responsibility. Then we do have the oversight and investigative responsibility, which we are conducting today through this hearing, asking again HHS why they are not following through with the recommendations.

There are two ways they can do that. One, within existing authority, or if they need additional resources to make certain these things are in place.

Now, Mr. Curtin has talked about another issue which extends beyond the informed consent but may need some type of tweaking in our laws as far as privacy or disclosure, and that is of course the subject of big discussions now with the tremendous amount of raw information that is coming out about folks.

He raises a certain concern. We have heard an abuse here that we may either need to address through regulation or legislation.

Dr. AMDUR. The IRB system failed to do what should have been done in his case. There is no question about that. We don't need a new system, we just need the IRB at MCV to have functioned the way it should have functioned.

Mr. MICA. Many of the IRBs, though, are sort of self-regulating, without a lot of protections. We are going to submit to the doctor and some others instances, but mostly we are reading about it in media accounts of conflict of interest.

In our last hearing, we also heard problems ranging in conflict of ethics to having some self-interest in proceeding with the human testing. Again, you are dealing with boards that basically have some interest in participating and moving forward, taking Federal funds for that activity, as opposed to closing it down or not proceeding and not receiving the funds.

Then the other problem we have is the huge explosion of all of this. It was just a few doing the testing some time ago. Now we are probably looking at thousands and thousands, plus the commercial and private side, where you do not have Federal funds and we have some loopholes in that regard.

What about mandatory registration of IRBs?

Dr. AMDUR. We need that. That is part of the request of extending the regulations of the Common Rule to all research. The reason that you don't know or nobody knows how many IRBs there are in the country is because the only record of an IRB is if they conduct FDA-regulated research or HHS-funded research.

We need to just simply fix that problem. I don't know that HHS can do that. I think it requires a higher level of mandate to pass a Federal law. I don't know that. But the point is, we need to extend the system of protection. Part of that would be a formally certified IRB according to the Common Rule regulations. Then we would not only know how many IRBs there are, but have some common system that they work under.

Mr. MICA. Let me ask Mr. McCarthy. You have looked at the Data Safety Monitoring Boards, DSMBs. Do you feel there should be some accreditation or additional regulation mandatory?

Mr. MCCARTHY. Yes, I would like to see some criteria established and required to be implemented. The criteria should state under what circumstances the Data Safety Monitoring Board should be established, what its authorities and responsibilities should be, and what its relationship to the local IRB should be in the centers where research over which it has oversight is being carried out.

I do not know whether that can be carried out under present legislation or whether it would require new legislative authority, but I think it is very important, and will be a major step forward if that should occur.

I agree with Mr. Curtin, that a kind of cookie cutter approach to informed consent is just what we don't need, because anything that routinizes informed consent, tends to rob it of its important meaning.

What I would like with respect to informed consent is to see the Department of HHS spending some money to do research on how to communicate risks and benefits associated with research more effectively.

We have a whole new generation of young people coming along who operate much more out of visual cues than out of written cues. To hand people a written, fairly complex document may not actually inform them of very much, whereas a videotape showing the same information might be much more effective.

In order to develop that kind of technology, somebody needs to sponsor some imaginative research into how to better inform subjects so that they will know and understand the consequences of their decisions to participate or not to participate in research.

Again, I don't know if you need a legislative mandate to carry that out or whether you simply need additional budget resources to carry that out, but I certainly think that ought to be a major function of the new office that is being created in HHS.

Even if a new approach to informed consent can be done without new legislation, it certainly cannot be done without additional money, so I would encourage that the Congress bite the bullet and provide the money so that imaginative new ways of communicating with research subjects can be developed and employed, and so that IRBs have a range of ways of communicating the risks and benefits of research to their subjects in meaningful ways. I believe we can respect the dignity of subjects more than we do at the present time with rather complex, long, written consent documents that may not do what they are intended to do.

Mr. MICA. Mr. Curtin obviously had a negative experience with the OPRR process. I think he recommended some solutions for corrections.

Maybe you could give us those again, Mr. Curtin.

Mr. CURTIN. Yes, sir. No, I did not have a negative experience with OPRR. The only thing that even could be remotely called negative about it was that it took them almost a year to get around to doing anything with my complaint. But once they did it——

Mr. MICA. That I would interpret as a problem.

Mr. CURTIN. That is, yes. But once they got on it, they were great. They kept me informed.

Mr. MICA. They did?

Mr. CURTIN. They did. They took some very, very severe action. They closed down 1,100 research projects at Virginia Commonwealth University.

Mr. MICA. Your difficult experience was getting attention at the beginning.

Mr. CURTIN. Right. They explained that to me right off the bat. They said, it is going to be a year before we get around to doing this. A year later I heard from them. I would have liked it to have been sooner, but I understand those kinds of things.

Mr. MICA. With the IRB process, you also were critical of the response you got there.

Mr. CURTIN. From the chairman, yes. Yes.

Mr. MICA. You——

Mr. MCCARTHY. Mr. Chairman, just to fill in that story, because maybe even Mr. Curtin does not know this, but after OPRR took its action, Virginia Commonwealth University hired me, and I have been working about 40 or 50 hours a week since January to educate investigators about their obligations on informed consent and to instruct potential new members of the IRBs.

So they are taking the criticism very seriously, and I expect that within a year they will have a system that will be as good as any in the country.

Mr. MICA. But it did take a year to get action. What did they say, they could not get to it?

Mr. CURTIN. They were overworked, backlogged.

Mr. MICA. OK. All right.

Mr. MCCARTHY. As a former Director of OPRR, I can say that is a perennial problem. I think the office has always been understaffed and underfunded.

Mr. MICA. I am also trying to find out what their recommendations were to us. They have to come to Congress to ask for additional funding through the appropriations process. If we have a deficit there and we have a larger scope of responsibility, we need to see that that is met. Maybe these 1,100 operations should have been closed down after the complaint was made, not a year later.

Again, we are just trying to look at where the problems are and what is going wrong and how we correct them. It is a pretty simple process, except I have to get 534 other people to agree on how to fix it.

Mr. CURTIN. If I might add, sir, the IRB there, they just did not take me seriously. It was as simple as that. They thought they would write me a letter and I would go away.

Mr. MICA. All right.

It sounds like we have at least Mr. McCarthy and Dr. Amdur's wealth of experience and recommendations. You have a personal experience.

I wanted to ask about some recommendations. I didn't make good notes on who said what, but you said consolidate sets of regulations. You cited HHS, FDA, education, and some standards. My staff just gave me the Department of Veterans Affairs standard for protecting human research participants.

Did you mean in the context again of protection, some standards that are protections for human research participants, no matter what the Federal agency?

Dr. AMDUR. Yes, exactly. What I meant was not an abstract thing, but an administrative one, meaning that if you look in the Code of Federal Regulations at 45 CFR 46, you will see HHS regulations.

Mr. MICA. Right.

Dr. AMDUR. If you look at 21 CFR 50 and 52, I guess it is, 56, you will see FDA. Most of it, 90 percent of it, are the exact same words. They are just copies.

But then in the remaining 10 percent of this situation, the regulations are different or they are silent on certain situations. There are many examples of that. The Department of Defense has certain requirements, and you know if they sign on to the Common Rule, then they do.

The point is that, for example, this adverse event reporting which you have heard so much about, this is the No. 1 workload problem for IRBs. It is the most ridiculous thing. There are boxes and boxes coming into the University of Florida's IRB every week of irrelevant reports that the IRB cannot possibly make any meaningful determination of. It may be a horrible adverse event that is

critically important, but because of the things Dr. McCarthy said, the nature of what you need, you need data in safety and monitoring, but the IRB should not be looking at those. Does the IRB need to do that? The regulations say they need to.

HHS regulations say certain things that can be interpreted certain ways. FDA regulations say very different things that likewise are interpreted very differently. So what I do on the IRB is sit around every week as chair of an IRB before coming to the University of Florida and try and say, how do we interpret this? Every year we have major discussion sessions at the national meetings: Well, how do we interpret this? And we are scared to turn away these things if there is any question that we need to be stamping them because we are scared of the regulatory consequences.

So the point is, what should be done is to say we are only going to have one set of regulations, and it would be very simple. There are people that sit around, and this is all we have thought about and discussed and written papers about, who can suggest and hammer out revised regulations where necessary that make them congruent, just like any revised regulatory process goes. But the thing we need is to say we are only going to have one set of regulations, and it does not matter what agency sponsors the research.

I would say we need to extend it. It does not matter if it is privately funded, and I think we need a law for that, not a Federal regulation. But the point is that we only need to have one set of regulations. That is what I mean when I say "standards," regulations that describe the standards: Say you need to go through an IRB. You need to have informed consent under these situations. Here is the form of the informed consent, that situation. We need just one of those.

The Common Rule does need a little polishing here and there, but it is basically what we would all come up with if we spent a long time thinking of standards in a regulatory system. It is a good system, and——

Mr. MICA. Are you aware of any formalized document or anything that has been prepared that proposes that and has language that would be acceptable to the vast majority of those who participate?

Dr. AMDUR. I think that when you say "vast majority" the people who are objecting to consolidation of the regulations——

Mr. MICA. We are not going to get everyone to agree.

Dr. AMDUR. Right, but the people who are objecting are the people in the agencies that want to keep their own regulations. Certainly industry sponsors, they just want to figure out: What do I need to do? They don't care what it is. It is so much better if they can just figure out what it is.

The International Council on Harmonization would be the closest thing to the answer to your question in that there is now. In order to make it so that companies, pharmaceutical companies, can do business in all different countries, there is a body that has done exactly what you have said, which is establish that we are going to have one uniform requirement. If you want to do business within this group, we are just going to say everybody has to comply with these regulations. We are not interested in your HHS or whatever. If HHS is the exact same, fine. All we know is, here is one set.

You know, I think that comes very close to what you are saying, but it would not be very difficult to come up with the one set. I think what is needed is some mandate at a higher level to say, come up with one set.

Mr. MICA. Mr. McCarthy, you wanted to respond?

Mr. MCCARTHY. I had some years' experience in OPRR, and of course we tried to do exactly what Dr. Amdur is suggesting; to come as close as humanly possible to a single set of regulations that would apply to all research, whether FDA-regulated or federally funded. We had no authority to reach out to that research which was neither FDA-regulated nor federally funded, so that problem I think is one that requires some congressional action to extend the authority of these offices.

But I think the problem is more complex than you have heard. Each agency has its own authorizing legislation, and it is that authorizing legislation that allows it to issue regulations. That legislation differs dramatically from FDA to Department of Defense to HHS to Department of Education.

Different congressional committees handle that legislation and draft it, so when you try to write a common set of rules that comply with a vast variety of laws, it is not a simple matter to write a single rule that complies with all of the authorizing legislation of all of the Federal agencies.

We did the best we could, and I would disagree, I think between HHS and FDA, the congruency is about 97 percent. What I would point out, however, is that FDA has authority for implementing its rules, and that means different people are doing it, and sometimes they interpret the rules a little differently.

That is why I would like to see this new HHS office become at least an HHS-wide office, and I would like the new office to have enough authority so it can be the lead agency to bring the other departments and agencies—that do less research but still a lot of research—into congruence so far as possible, given the plethora of laws that govern them.

I think much more can be done, so I am agreeing with Dr. Amdur's point, but I think it is not a simple issue. This is a situation where the Congress itself, by placing certain kinds of goals for the new HHS office and providing it with resources to accomplish those goals, could go a long way toward accomplishing what he wants. I doubt if it can ever be perfect, but we can do lots better.

Mr. MICA. Dr. Amdur wanted to respond.

Dr. AMDUR. You know, Dr. McCarthy has worked in the government too long, because now he is making excuses for it. You know, our role here is simply to say what needs to be done and for you to figure out how to do that.

We need a common set of rules, and we do have plenty of models for that in the research world. For example, in 1996 Congress passed the Health Insurance Portability Act. As part of that, it required legislation to be passed that set standards for the protection of privacy of access to the medical record.

Federal law said this has to be done. It did not say "unless FDA objects to it," or the FDA—"unless it conflicts with FDA's view of it." It said, that is it. America, that is the way it is going to be done. A Federal law passed.

We are about to see a law go into effect that supersedes all of our other research baloney of interpretation, of how do we interpret HHS, how do we do that. It is going to be a problem, of course, to implement it because there are problems with the way that law is written. But the point is that mechanism is there to say that, well, research, this is the way it is going to be done, regardless of one Federal agency's policy or another.

I think that we can solve this problem.

Mr. MICA. I am probably somewhere in between the two of you.

Mr. MCCARTHY. We are not very far apart. We have exactly the same goal.

Mr. MICA. Mr. McCarthy has described a political situation of congressional authorization, and there is not just the agency turf jealousy. We also have the committee authorizing jealousy, and to get them to all agree on anything is very difficult.

I see your point, though. We have, as you pointed out, in other legislation required some standards. I think everybody agrees that there should be informed consent. I think everybody is agreeing now there should be some registration of at least the IRBs, right? And then we get into some other areas.

We have not really talked about accreditation or certification for IRBs or DSMBs. Dr. McCarthy, what do you think about some accreditation or certification standard?

Mr. MCCARTHY. I strongly endorse this effort. As a matter of fact, I have been selected to serve on the board of the new organization that Dr. Amdur cited, and I am dedicated to trying to bring this about as best we can.

Mr. MICA. Should that be voluntary or mandatory?

Mr. MCCARTHY. I think that it ought to be voluntary and supplemental to the kind of oversight exercised by the government. I think we have an excellent model in the Association for Accreditation of Laboratory Animal Care, Int. I think it has worked very well for many years as a supplement to government efforts.

Mr. MICA. How long has that been in place?

Mr. MCCARTHY. At least since 1970, and if memory serves, about 1965, but a very long time. It has worked exceedingly well, and one of the people serving on the new AAHRPP board is the director of AAALAC, so that we are able to profit from his experience and his guidance.

I think the one thing holding up accreditation is funding, and we are now seeking some funding sources in order to get this corporation off the ground. We think it will be self-sustaining because it will be in the best interests of the institutions to be accredited, to get a Good Housekeeping Seal of Approval on their programs, before OPRR or FDA or some other agency comes in and shuts down their research. This way we can make a supplemental contribution to what the government is doing.

In no way would I weaken the government's authority or the extent of its oversight, but I think human subjects are so important that we can supplement what government can do and head off many problems before they occur.

Mr. MICA. Dr. Amdur, what about certification or accreditation?

Dr. AMDUR. I think that it needs——

Mr. MICA. Give me your ideas on how that should be accomplished.

Dr. AMDUR. A program that will work very well for this purpose is not in the planning stages, it is in the very end stages of the planning and about to be implemented by PRIM&R. This is the AAHRPP program. In three pages in the written testimony we explain the mechanics of it.

Very briefly, what you do first is—this is about to be completed—you organize a group of experts that then write down basic best practice guidelines for the fundamental aspects of a system of protecting human subjects: The institution, the IRB, education of investigators, management of adverse incidents, etc. You start there, and that has been done.

Then you have a written phase where the institution responds to their current status related to those. Then you have an onsite investigation where usually two or three experts go to the institution and have to interact with all the key components of the system and see how it is really working according to objective and there are some subjective aspects of it, and issue a grade, if you will, of the institution related to a whole checklist of things.

If the institution meets certain standards, which are outlined in the program, then they get the accreditation for 3 years is the proposal. So PRIM&R has been working very hard to indeed hammer out the details. It is not perfect yet. It has not been tried in the field yet. Like any system, it will obviously iterate and evolve and change and be polished as it is used. The more support it gets, the quicker it can get online, but it is ready to go.

I would strongly support a model that is that far along already to get out into the field and get going.

We have to accredit everything we do. You go and get the gas tank filled for your gas grill and the people that fill the gas have to have a certification. We need an accreditation process for the protection of human subjects, and that is something that is really long overdue.

Institutions will not balk at this, they will embrace it. They want to know, what do I need to do to be doing things correctly. They will embrace it if it is a credible system that is tagged to meaningful evaluations. If it is just an audit system of a bunch of accountants going and checking and looking for pieces of paper that say certain things and the date matches this date, you know, they will do it if they have to because the experts on protecting human subjects are the investigators, in most cases. They know if the IRB is asking the meaningful questions. They know if the institution is providing the right environment to support them and be able to resist conflicts of interest.

As long as it is a meaningful, credible process done by people who know what they are doing, the institutions will embrace it. But it needs to be supported as widely as possible.

Mr. MICA. Do you endorse the mandatory versus voluntary?

Dr. AMDUR. I am scared to say yes, mandatory, because we should always have as little required regulation as possible. I just need to see the exact format of how that requirement would be, because when we actually write it down and see how it is implemented, I am concerned.

I think it will be enormously effective even if it is voluntary and if the regulations required—I personally right now, don't think it has to be a mandatory, required system. I think HHS regulations and authority already have the authority to put the pressure, as they are trying to do, on institutions to do things correctly. The institution will seek out ways to find out what is correct and improve their system on their own if they are indeed under a regulatory system that evaluates the end point.

So I think they will seek the accreditation process on their own and there will be other forces that end up requiring it. For instance, industry will require it. Once there is any meaningful system in place, industry sponsors will require it. They will say, we are not dealing with you unless you are an AAHRPP-accredited institution. So I don't think it has to be mandated at the Federal level.

Mr. MICA. I have additional questions we may submit some to you and some of our other witnesses today, but I think we have just passed the 6 o'clock hour.

I do want to thank each of you for participating, for being with us this afternoon, for your contribution in helping us improve this entire process, and also the Federal agencies that are responsible for implementing law and Federal policy.

There being no further business to come before the subcommittee—and again, I want to thank you for your participation and willingness to provide us with your personal experiences and your expertise on this important issue—this hearing is adjourned.

[Whereupon, at 6:02 p.m., the subcommittee was adjourned.]

[Additional information submitted for the hearing record follows:]

Oversight Hearing Follow-Up Questions For the Record - May 3, 2000
Gary Ellis, Ph.D., Acting Director
Office for Protection from Research Risks (OPRR)
National Institutes of Health

(1) When did NIH become aware of this event?

The subject was admitted to the NIH Clinical Center on 6/1/99 with aplastic anemia. This was reported to the Institutional Review Board (IRB) orally on 6/7/99. The subject expired on 6/14/99 at the NIH Clinical Center. The National Institute of Allergy and Infectious Diseases (NIAID) IRB was notified that same day.

(2) How was NIH notified?

Notification of the death of this subject was reported promptly by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (N IAMS) Clinical Director to the Chair of the NIAID IRB on 6/14/99, the date on which the subject expired. Steps to be taken were reviewed and enrollment in the protocol was suspended.

(3) How and when did OPRR become aware of this event and why wasn't OPRR notified by NIH?

OPRR first learned of the death of the subject enrolled in the NIAMS clinical trial on March 15, 2000, when it received a telephone call from Sue Reinert, a reporter for the Patriot Ledger, asking questions about this subject's death. Additional details of this event became known to OPRR when it received a copy of the March 24, 2000, Patriot Ledger article on about March 28, 2000.

This death was not reported to OPRR by NIH in a timely fashion. NIH has recently revised its adverse event reporting procedures for its Intramural Research Program to ensure timely reporting of adverse events to OPRR. Although procedures have always been in place requiring timely reporting to the IRB, we have reminded IRBs that (1) all unexpected serious adverse events shall be reported in writing to the NIH Office of Human Subjects Research (OHSR) within 14 days after the evaluation is completed by the IRB, and (2) all other unexpected adverse events will be summarized and reported to OHSR following continuing reviews by the IRB. OHSR will, in turn, report these events to OPRR. We are confident that these procedures will prevent the oversight that occurred regarding this particular event.

(4) Was the FDA notified of this event? If not, why not?

Yes, the FDA was notified. A memorandum was sent by NIAMS to the FDA by express mail on June 15, 1999, to notify them that a death had occurred.

Oversight Hearing Follow-Up Questions For the Record - May 3, 2000
Gary Ellis, Ph.D., Acting Director, Office of Protection for Research Risks (OPRR)
National Institutes of Health

(5) Did OPRR conduct an investigation of this event?

OPRR has initiated a compliance oversight investigation of this matter.

(6) Did the FDA participate in the investigation of this event?

FDA is not participating in the OPRR investigation of this matter.

(7) What are OPRR's findings, particularly those related to the institution's adherence to their IRBs assurance?

OPRR has not made any determinations or issued any findings. The inquiry described above is underway.

(8) Did NIH researchers have prior knowledge about possible problems with using fludarabine?

The informed consent document from the beginning of the trial described all reasonably foreseeable risks and discomforts. All subjects were made aware that fludarabine had caused strokes, paralysis of the legs and arms, coma and even death. Further, the consent form clearly stated that it was not known whether the dose used in this study could cause these problems. It also stated that this clinical research study might involve unforeseeable risks to the participants.

(9) Why did NIH researchers ignore the medication's warning label that tells patients they should receive only irradiated blood if they needed a transfusion?

To be specific, the package insert stated that transfusion-associated graft-versus-host disease has been observed rarely after transfusion of non-irradiated blood in patients treated with fludarabine and that consideration should be given to the use of irradiated blood products in patients undergoing treatment with fludarabine. Prior to this protocol, NIAMS participating physicians had previous experience with fludarabine in the treatment of psoriatic arthritis and membranous glomerulonephritis. Furthermore, an outside expert was consulted and asked to comment, based on her experience with fludarabine, on any known consequences of this drug. The investigators carefully reviewed the literature and known trials before composing the protocol and the informed consent in which consequences of fludarabine therapy were addressed. At the time of the initial protocol, there were no known reports of transfusion-associated graft-versus-host disease in patients other than those with leukemia. In addition, no cases of transfusion-induced graft-versus-host disease had been reported in any lupus patient despite therapy with numerous drugs used in cancer chemotherapy. The aim of the study was to establish the tolerance and toxicity of the proposed regimen of cyclophosphamide and fludarabine in patients with lupus

nephritis. Doses of both agents were modified to avoid profound bone marrow suppression.

(10) Why weren't patients and their doctors informed of this warning until after the patient's death?

At the time of the initial protocol, there were no known reports of transfusion-associated graft-versus-host disease in patients other than those with hematologic malignancies. In addition, no cases of transfusion-induced graft-versus-host disease had been reported in any lupus patient despite therapy with numerous drugs used in cancer chemotherapy. In fact, the diagnosis of graft-versus-host disease was not confirmed until the fall, several months after the subject's death. However, based on the investigators' clinical judgment, they alerted patients and physicians of the possibility of graft-versus-host disease in June, shortly after the subject expired.

(11) How many clinical trials involving fludarabine are in progress at this time?

The NIAMS does not have any fludarabine studies at this time. The NIH Intramural Research Program currently supports 11 active protocols that use fludarabine.

(12) What has OPRR done to identify ongoing similar research?

To date, OPRR has not taken any steps to identify ongoing similar research.

(13) Has OPRR suspended similar or related trials as a result of this event?

No.

(14) How will OPRR prevent further tragic events of this nature?

OPRR provides educational guidance to research institutions and negotiates trust agreements (called "Assurances") with research institutions covered by the regulations for protection of human subjects of the Department of Health and Human Services. These steps strive to minimize the possibility of harm to research subjects.

(15) What action, if any, has NIH taken in regard to the lead investigators who were conducting these trials?

Following the adverse event, a thorough review of the documents related to this protocol was conducted and NIH determined that the investigators did their utmost to ensure that risks to subjects were minimized. OPRR is still completing its review of this matter. NIH will consider carefully any recommendations from OPRR.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

MAY 30 2000

The Honorable John L. Mica
Chairman, Subcommittee on Criminal Justice,
Drug Policy and Human Resources
House of Representatives
Washington, D.C. 20515

Dear Mr. Mica:

Thank you for your letter of May 5, 2000, posing follow-up questions from your hearing of May 3, 2000. We include the list of questions as an attachment and below we offer our responses to them.

QUESTION 1 - Has the Department of Health and Human Services (HHS) indicated they require additional personnel and resources to implement your recommendations?

ANSWER - On May 23, 2000 the Department issued a press release announcing that Secretary Shalala is bolstering protections for human research subjects. The new initiatives are intended to further strengthen protections of human research subjects in clinical trials including those involving gene transfer research. The press release goes on to say that "More resources may be needed to fully implement these responsibilities in the years ahead."

QUESTION 2 - Has HHS committed to a date or dates certain for implementing your remaining 1998 recommendations?

ANSWER - The Secretary's initiatives go a long way to meeting the recommendations we made in our 1998 report addressing the following issues: education and training; informed consent; improved monitoring; and conflict of interest. Furthermore, in recent weeks, HHS has given serious attention to our specific recommendations and their implementation. While we do not have a schedule of dates as of yet, we view the Department's new initiatives as an encouraging development that could lead to considerable progress in improving Federal oversight of human subject protections.

QUESTION 3 - In your estimation, what actions could HHS have taken to implement your recommendations, which would not require a significant expenditure of funds?

ANSWER - We recognize that many of our recommended reforms would require resources at either the Federal or local level, or both. However, some of the recommendations would require minimal expenditures. Among them are: eliminating or lessening some of the procedural requirements; requiring sponsors and investigators to notify the Institutional Review Boards (IRBs) of any prior review; requiring more

extensive representation of nonscientific and non-institutional members on the IRBs; reinforcing the importance of IRBs maintaining sufficient independence; and, prohibiting equity owners from participating in the IRB review process.

In addition to these measures, at least two elements of the Secretary's new initiatives can be implemented without additional legislation or rule making and at relatively low cost to all parties — education and monitoring. Education and training could begin easily by making the Department's own considerable educational materials, which are now used internally, available to external clinical investigators, IRB members, and associated IRB and institutional staff through the internet and other means. Part of the new improved monitoring initiative could begin by implementing the requirement that investigators conducting smaller-scale early clinical trials (Phase I and Phase II) submit clinical trial monitoring plans to the National Institutes for Health (NIH) at the time of grant application and share these plans with IRBs. Since NIH already requires that they have such plans in place, submitting them will not require additional time and effort on the part of investigators.

QUESTION 4 - What organizations and persons comprise and how large (quantify as accurately as possible) is the universe of private sector human subjects research currently underway in this country?

ANSWER - At this time, there are no authoritative data that documents the size of this research sector. However, we have found this to be a growing portion of the research community. The Pharmaceutical Research and Manufacturers of America estimate that private pharmaceutical companies have tripled their world-wide research and development investment between 1990 and 1999 from $8.4 billion to $24 billion. And industry reports show that in 1995, there were 2,585 drugs in pre-clinical testing; by 1998, that number had risen to 3,278. Private sector research is conducted by both academic medical centers and private sites, such as doctors' offices or dedicated research sites.

The fifth to eleventh questions posed questions on conflicts of interest— its prevalence and oversight. We have not undertaken an inquiry in this area, and thus we cannot speak to these issues with any expertise. However, we share your concern about the potential influence of conflicts of interest on the research process. That is why a number of the recommendations in our 1998 report focused on moderating potential conflicts on IRBs.

Thank you again for the opportunity to speak at the oversight hearing. We appreciate your interest in human subject protections issues. I hope this information is responsive to your questions and concerns. If I can answer further questions, please contact me directly at (202) 619-0480 or have your staff contact Elise Stein at (202) 619-2686.

Sincerely yours,

George Grob

George Grob
Deputy Inspector General
for Evaluation and Inspections

Attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Assistant Secretary
for Legislation

Washington, D.C. 20201

August 7, 2000

The Honorable John Mica
Chairman
Subcommittee on Criminal Justice, Drug Policy and Human Resources
Committee on Government Reform
B-373 Rayburn Office Building
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

Please find attached the requested responses to your questions on human subjects protections, which were addressed to Dr. William Raub, Deputy Assistant Secretary for Science Policy. As you know, there has been significant ongoing activity by the Department in recent weeks regarding oversight of Institutional Review Boards (IRBs) and protection of human subjects in clinical trials.

In June, after we received your questions, the human subjects protection functions within the former Office for Protections from Research Risks (OPRR) were transferred from the National Institutes of Health (NIH) to the Office of the Secretary. That office was renamed the Office of Human Research Protections (OHRP). After a rigorous and thorough selection process involving a number of qualified candidates, Dr. E. Greg Koski was selected as the new head of OHRP. Dr. Koski has an outstanding scientific background in human subjects protection oversight.

Dr. Koski is now working with the Office of the Surgeon General to formulate his office's goals for expanding rigorous safety measures for the IRBs which OHRP is responsible for monitoring. The Department will seek additional resources and professional staff for his office and its enhanced responsibilities, as detailed in the attached responses.

Dr. Koski has informed my office that he would be pleased to personally meet with you at your convenience to discuss OHPR's plans for improving protection of human subjects in clinical research, and oversight of the nationwide system of IRBs. You have been sent, under separate cover, a letter from the Secretary, addressing your questions about Dr. Koski's selection and other issues involving OHRP. We look forward to working with you further on these matters.

Sincerely yours

Jane Horvath for

Richard J. Tarplin
Assistant Secretary for Legislation

OVERSIGHT HEARING FOLLOW-UP QUESTIONS

William F. Raub, Ph.D.
Deputy Assistant Secretary for Science Policy
Department of Health and Human Services (DHHS)

1. Why hasn't HHS implemented each of the OIG's 1998 recommendations? Which recommendations are difficult to implement and why? When will all of the OIG's recommendations be implemented?

Although a substantial amount of work remains to be done, the responsible DHHS entities have taken important steps since June, 1998 to improve the system of protections for human research subjects. These activities are summarized in the Attachment to this set of answers.

The most difficult recommendations to effect are those that might require modification of the "Federal Policy for the Protection of Human Subjects", also known as the "Common Rule" (for DHHS, 45 CFR 46) – the regulation issued jointly in 1991 by 17 agencies of the Federal Government. Gaining unanimous agreement from 17 agencies to change the Common Rule could be an arduous task. The OIG report of April, 2000 acknowledges this problem and suggests that new legislation may be the appropriate remedy.

If implementation of particular OIG recommendations cannot be done without amendment of the Common Rule or passage of legislation, the process could require several years. For example, gaining agreement of the 17 agencies regarding the Common Rule spanned a decade. Otherwise, DHHS should be able to address the bulk of the OIG's recommendations appropriately within 12-18 months.

2) OPRR's primary method of oversight is through the assurance process. It seems as though this process is perfunctory. Are more actual inspections by OPRR needed? Is this practical? Explain what should be done.

More inspections by OPRR are warranted, and this is an attainable objective. In the course of simplifying its assurance process (see Attachment, Item 6a), OPRR will require education of institutional officials, IRB staff, IRB members, and investigators relative to human subject protection requirements. In addition, OPRR plans to increase dramatically both (i) the number of not-for cause site-visits to assured institutions, and (ii) the number of not-for-cause reviews of institutional procedures for protection of human subjects.

3) The OIG states that OPRR's limited inspections are based primarily on complaints or concerns about compliance. Is HHS developing a more systematic and proactive method of inspection and investigations based on a systematic identification of adverse events and institutional lapses?

Yes. OPRR intends to develop a more systematic and pro-active method of inspection and investigations. In addition, NIH has instituted a program of not-for-cause site visits to review compliance with various NIH policies, including data and safety monitoring. NIH plans to conduct 10 such visits per year. The first three were completed recently.

4) While the OIG credits NIH and its Office for Protection from Research Risks with increasing onsite investigations from 1 to 10 over the past two years, NIH reports that since 1990, the OPRR has undertaken compliance visits to only 125 institutions. With assurances from over 4000 institutions, why so few site visits?

For-cause compliance site visits are extremely labor and resource intensive. OPRR has 178 compliance oversight investigations currently in progress. However, OPRR intends to increase its investigations and inspections as resources allow.

5) FDA's on-site investigations of IRBs increased from 253 to 336 during the same time period? What triggered these investigations? Were they coordinated with OPRR? Were the results of these investigations shared with OPRR? Why has FDA made so few on-site investigations? What do FDA visits examine, and how does this compare with OPRR visits?

FDA's increased number of inspections in FY 99 resulted from a determination that some could be supported through user fees. Although FDA inspections are not "coordinated" with OPRR, the results of the inspections are shared with OPRR. FDA does not consider 336 inspections in a year to be "few"; it represents a sample size of about eight percent of all IRBs. FDA plans to further increase such inspections, if the President's budget request is fully funded in the FY 2001 appropriation.

FDA inspections of IRBs trace one or more studies through the review process to get a good understanding of how the IRB operates. FDA examines: the IRBs written procedures to determine if they are adequate and being followed; documentation of IRB activities (e.g., minutes of meetings); the product of the IRB review (e.g., approved consent forms); and the IRB's continuing review of research.

FDA is responsible for reviewing the operations of IRBs related to the review of research on regulated products--drugs, devices, biologics--for which the sponsor has submitted a research or marketing application to the agency, or other information received by the agency. The sponsor is the entity or individual who initiates and takes responsibility for the conduct of the research. FDA shares information wherever possible, for example via quarterly meetings, with OPRR and

consults on controversial problems and issues related to institutional review boards. Given the different statutory and regulatory responsibilities, however, each agency carries out its own inspection program. When OPRR inspects a particular IRB, OPRR generally notifies FDA if there are irregularities related to FDA's jurisdiction for evaluation and follow up and vice versa.

During an on-site FDA inspection of an IRB, the FDA investigator will examine the IRB's operations and records to determine if the IRB is in compliance with the regulatory requirements for IRBs outlined in 21 CFR 56. For example: Does the IRB have at least 5 members with varying backgrounds (including a physician) that will ensure complete and adequate review of research conducted at the institution? If the research involves a vulnerable group of subjects (prisoners, children, mentally disabled persons), does the IRB include a member who is knowledgeable about and experienced in working with these subjects? Does the IRB keep and maintain records (minutes) about its meetings? Do the minutes show the basis for requiring changes in or disapproving research? Are those minutes detailed enough to show attendance, voting, discussion and resolution of controversial issues? Additional detail is available in FDA's standard operating procedures for its investigators, contained in the Compliance Program Guidance Manual, Chapter 7348.809, "Institutional Review Boards." (on FDA website)

6) Given that OPRR has assurances from over 4000 institutions and only 87 of these institutions reported adverse events, are adverse events underreported? Is NIH's report of 0 adverse events for this time period accurate?

Investigators sometimes fail to understand, and thus fail to fulfill, their obligation to report all "unanticipated problems involving risks to subjects or others" to their IRBs, as required by the regulations. Further, institutions sometimes fail to report all such unanticipated problems to OPRR, as required under the regulations. This problem will be addressed as part of the continuing reform of DHHS oversight of human subjects research. NIH has revised its procedures to ensure timely reporting unanticipated of problems.

7) Minimal progress has been made in recasting federal IRB requirements so they grant IRBs greater flexibility and hold them more accountable for results. What has HHS done to eliminate or lessen requirements that are of questionable value?

Relative to recasting Federal IRB requirements, OPRR (i) expanded the research categories that may be reviewed using expedited procedures (in cooperation with FDA); (ii) harmonized its guidance with that of FDA to permit IRB meetings to be convened via telephone conference calls; (iii) issued guidance permitting IRBs to utilize Data and Safety Monitoring Board (DSMB) reports in the continuing review process; and (iv) expects to implement plans for a simplified and streamlined Assurance process by the end of this calendar year. Additional IRB flexibility with increased accountability will require development of performance based standards for IRB activities. Development of such standards is proving quite difficult. OPRR is working with Public Responsibility in Medicine & Research (PRIM&R) to develop accreditation procedures for IRBs that will utilize performance based standards.

8) Continuing IRB review is a low priority at many IRBs, and some IRBs have little knowledge of what actually occurs during the consent and research process. Why hasn't HHS adopted accreditation and/or certification as a requirement of IRBs and their members? Could HHS move forward on accreditation/certification now?

A successful accreditation program requires, at a minimum, a set of widely accepted performance standards and at least one private-sector organization with sufficient competence, resources, and commitment to be deemed by DHHS as an accrediting entity. OPRR is working on accreditation procedures as indicated in the response to the preceding question. To seek to identify potential private-sector accrediting entities before standards and procedures are in place would be premature.

9) According to the OIG the most important continuing protection for human subjects is the presence of well-trained and sensitive investigators and IRB members. Why haven't educational requirements been established and enacted for investigators and IRB members? Could HHS require a minimum educational requirement now?

DHHS regulations require that sponsors select "qualified investigators" (21 CFR 312.50); and that the "IRB shall be sufficiently qualified through the experience and expertise of its members...to promote respect for its advice and counsel..." (21 CFR 56.107(a), and 45 CFR 46.107(a). Otherwise, DHHS has not prescribed specific educational requirement and heretofore believed that voluntary educational programs for investigators and IRB members were sufficient. DHHS now believes that specific educational requirements are indicated. To that end, OPRR's simplified Assurance process will require education of institutional officials, IRB members, and investigators relative to human subject protection requirements. Moreover, beginning in October 2000, the NIH will require investigators engaged in clinical research to obtain education in the fundamentals of protection of human subjects. NIH will review the credentials of these investigators before funding is made for their projects.

10) The increase in private sector human research and the competition for research dollars obviously heightens the opportunity for competition and conflicts of interest. Why hasn't HHS moved to broaden and increase community representation on IRBs?

Heretofore, DHHS found it sufficient to allow IRBs to decide for themselves the nature and extent of community participation over and beyond that which is required by the Common Rule and FDA regulations. OPRR is considering developing guidance calling for more representation on IRBs of nonscientific and noninstitutional members. Requiring more representation could entail modification of the Federal Policy (Common Rule) for the Protection of Human Subjects. If so, such a modification would require identical and coordinated rulemaking by 17 separate departments and agencies. In addition, DHHS is concerned about financial conflicts of interest and has scheduled a public conference on this topic for August 15-16.

11) It is obvious that IRBs are overworked and poorly resourced. What has HHS done to

lighten their workload besides adding "Data & Safety Monitoring Boards (DSMBs)?

In 1999, the NIH issued guidance on the reporting of adverse events for clinical trials. Because it can be difficult for IRBs to assess individual adverse events, this guidance requires Data Safety Monitoring Boards (DSMB) to provide IRBs with summary reports of their discussions of aggregated data on adverse events.

The NIH has recently implemented "just-in-time" IRB review of research protocols. Under this plan, investigators have the option to defer submission of their grant applications for IRB review until after they have received a peer review score that is likely to result in funding. This change in grants policy should reduce the work load of IRBs because most investigators are not likely to seek IRB review for projects that are not likely to be funded by the NIH. This change should allow IRBs to focus energy and resources on the review of studies that are very likely to be implemented.

In order to lighten the workload on IRBs, FDA is actively examining the current requirements that result in the IRB receiving boxes of reports of adverse events, with no analysis and no denominator that would enable the IRB to efficiently or meaningfully review the information to make human subject protection decisions. FDA believes that there are ways to ensure that the IRB receives important information that it needs without overburdening the system. This will, however, require a change in regulations. FDA has a working group looking specifically at this issue.

12) Minimal progress has been made in reengineering the federal oversight process. What specifically has HHS accomplished and what does it plan to do to hold institutions accountable for staffing and equipping IRBs? What has been done to improve and streamline the assurance process? What are OPRR's current budget and staffing levels? Has HHS requested increased staff for OPRR? What were the HHS FY 2000 budget requests to increase human research protections?

(a) Full implementation of the Federal Policy (Common Rule) requires adequate staffing of IRBs. OPRR has required corrective action where it has found such staffing to be inadequate. OPRR is working with Public Responsibility in Medicine & Research (PRIM&R) to develop accreditation procedures that will utilize performance based standards for IRBs that will require adequate resources.

(b) OPRR expects to implement plans for a simplified and streamlined Assurance process by the end of this calendar year. All of the current multiple, complex, legalistic Assurance documents will be eliminated and replaced with either a Federalwide Domestic Assurance or a Federalwide International Assurance covering all Federally-supported human subject research. Each will consist of one page of simple text, a list of institutional components, and designation of one or more IRBs. Each will also include requirements for institutional education and oversight programs. Assurances will be renewed every 3 years by electronic submission of a 1-page

renewal form.

(c) OPRR budget and staffing levels related to human subjects protections are approximately $2.4 million and 25 FTEs for FY 2000. While no specific programmatic increases were requested for this office within NIH at the time the FY 2000 Presdient's budget was formulated, HHS is committed to significantly enhancing resources for this function now that it has been relocated to the Office of the Secretary.

(d) DHHS has requested increased funds and staff billets for OPRR as part of the FY 2000 budget request.

13) The OIG and HHS have cited the Common Rule as a barrier to effecting change. Explain how the Common Rule slows or impedes change.

Because the Common Rule is codified separately for each department or agency that has adopted it, modification of the Common Rule requires identical and coordinated rulemaking by 17 separate departments and agencies. The wide variety of missions, program objectives, and Congressional oversight for the various agencies make unanimity difficult to achieve.

14) If this is HHS's rule and it prevents progress, why doesn't HHS exercise leadership and change it?

The Common Rule is not solely DHHS's rule. The Common Rule is codified separately for each department or agency that has adopted it. Thus, modification of the Common Rule requires identical and coordinated rulemaking by 17 separate departments and agencies.

15) What is the reason for the delay in other agencies not signing all parts of the Common Rule? What are the risks that result?

Seventeen Departments and Independent Agencies have adopted the Common Rule through their own rule making actions. Thus, each of them is responsible for interpreting and enforcing the rule within its area of cognizance. DHHS has no authority to require adoption of the policy by other Departments or Independent Agencies or to demand uniform implementation. Incomplete participation in the Common Rule and absence of uniform implementation among participants means, at least in theory, that the nature and extent of human subjects protection varies among programs of the Federal Government.

16) What is HHS doing to create a registry of IRBs?

All institutions receiving DHHS support for human subject research are already required to register the IRBs responsible for that research in the form of an Assurance to OPRR. For the IRBs within its cognizance, FDA has identified the information that would be collected during registration as well as the method of collection. However, implementation will require changes in the FDA regulations and sufficient resources. Neither FDA nor OPRR currently has authority to require registration of all IRBs in the United States. We are currently reviewing what legislation would be needed to do this.

17) A recent Los Angeles Times article alleges that the U.S. Government's top diabetes researcher helped guide a $150-million federal study involving Rezulin while serving as a paid consultant for the drug's manufacturer, the Warner Lambert Company. What is the Federal law governing outside employment of Federal employees and conflicts of interest? Does HHS's policy mirror the overarching federal law?

Federal Laws and Regulations- There is an extensive body of Federal laws and regulations governing outside employment of Federal employees and conflicts of interest. These include the following non-exhaustive list of authorities, which are available via the Office of Government Ethics web site (http://www.usoge.gov/usoge006.html):

Outside Employment

- Summary information from the US Office of Government Ethics (OGE).
- The *Standards of Ethical Conduct for Employees of the Executive Branch*, published by OGE, dated 9/30/99, specifically, 5 Code of Federal Regulations - Section 2635.801-809.
- 5 C.F.R. Part 5501 (formally codified at 45 CFR Part 73), HHS Supplemental Standards of Ethical Conduct for Employees.

Conflict of Interest

- Summary information from the US Office of Government Ethics.
- The *Standards of Ethical Conduct for Employees of the Executive Branch*, published by the OGE, dated 9/30/99, specifically, 5 Code of Federal Regulations - Section 2635.401-403.
- 18 United States Code - Section 208.

NIH Policy Guidance and Training - NIH takes very seriously the responsibility for implementing the *Standards of Ethical Conduct for Employees of the Executive Branch* and the ethics statutes. NIH ensures that all employees subject to the ethics training requirements receive their annual training. In fact, NIH provides a web-site dedicated to ethics, including web-based interactive ethics training. NIH also publishes two extensive policy and procedural manual chapters on ethics issues. The training and manual chapters are available via the NIH Ethics Program web site (http://ethics.od.nih.gov/):

- NIH Manual Policy Manual 2300-735-4 - Outside Work and Related Activities with Outside Organizations, published February 17, 1998.
- NIH Policy Manual 2300-735-1 - Avoiding Conflicts of Interest, published June 19, 1998.

NIH Procedures for Assuring Compliance with Outside Activity/Conflict of Interest Requirements

NIH employees wishing to engage in certain outside activities must complete an HHS-520, "Request for Approval of Outside Activity," and the NIH supplemental forms. The HHS-520 form captures information regarding the type of work, the outside organization, time frame, and type of compensation, if applicable. In addition, NIH developed two supplemental forms to accompany the HHS-520 to ensure compliance with audit recommendations. One unnumbered supplement form obtains detailed information about the topic and functions of the outside activity, specifically how the proposed outside activity differs from the employee's official duties. The NIH 2657 form provides detailed requirements for the employee to follow when engaging in consulting, testimony or legal practice, and professional health care practice with outside organizations. This form includes signature blocks for the employee to indicate compliance with the requirements. This information is reviewed to assess whether a conflict exists.

Outside activities which require prior approval are reviewed and approved/disapproved by a Deputy Ethics Counselor (DEC), the official in each NIH Institute or Center (IC) with authority delegated from the Department of Health and Human Services Designated Agency Ethics Official. The position of DEC is filled by the highest authority levels at NIH, for example, IC Director, Deputy Director, or Executive Officer.

The review and approval process for outside activities generally follows the steps below:

1. Employee completes the HHS-520 package including the HHS-520 form, the applicable NIH supplemental forms, an invitation letter or other communication from the outside organization, and any other pertinent information.
2. All forms and supplemental documentation are reviewed by the employee's supervisor and forwarded to the employee's Deputy Ethics Counselor (DEC).
3. The DEC or delegatee reviews and approves the request for outside activity based on the information presented, requests additional information, or disapproves it.
4. Copies of approved HHS-520s are returned to the employee, with a copy of the HHS "Notice to Applicant for Prior Approval of Outside Activities." This "Notice" contains advice on the employee's legal responsibilities when engaging in outside activities, including his/her responsibilities for avoiding conflicts of interests. (The "Notice" was mandated by the DHHS Office of General Counsel, Ethics Division, in January 1999.)

The same process is followed by senior NIH officials seeking approval to engage in an outside activity, i.e., IC Directors and IC Deputy Ethics Counselors. However, in these cases, the NIH Deputy Ethics Counselor reviews and approves/disapproves the activity request. The NIH DEC is currently the Acting Director, NIH.

18) In your opinion, does the NIH researcher's employment as a consultant with Warner Lambert pose either a conflict of interest or the appearance of conflict?

As you know, the NIH Director asked the HHS Inspector General (IG) to look into this matter. The IG reported to NIH on June 6, in pertinent part, as follows:

> "Our investigation of alleged conflicts of interest involving Drs. Eastman and Olefsky is closed.
>
> On May 8, 2000 the United States Attorney's Office for the District of Maryland declined prosecution after determining there was no factual basis to conclude that the subjects had any criminal intent regarding their activities at NIH. The U.S. Attorney's Office further determined there was no factual basis on which to conclude that the subjects made any false statements or participated in acts which affected their personal financial interests.
>
> As you are already aware, our investigation did uncover administrative errors which contributed to the appearance of a conflict of interest associated with Dr. Eastman's outside activities with Warner-Lambert Company. Notwithstanding these errors however, the investigation established that Dr. Eastman's outside activity requests were reviewed and approved in accordance with the internal NIH regulations in effect at that time."
>
> If the subcommittee wishes a copy of the report, inquiries should be made directly to the Office of the Inspector General, HHS.

19) This researcher is alleged to be receiving $150 per hour for his consulting services, how much did this person receive from Warner Lambert before and during the course of events that led to Rezulin's approval?

The IG has indicated that Dr. Eastman received $43,500 from Warner-Lambert and affiliated organizations (page 8 of IG report).

20) Did HHS conduct an investigation of this arrangement to determine if there was a conflict of interest?

As indicated, NIH requested the HHS IG to conduct such an investigation, which is now complete.

21) If so, what are the reportable findings of this investigation? Were any sanctions levied?

The IG findings have been summarized in the answer to question 18. The IG has indicated further that it will issue recommendations in a separate communication to NIH. Until that time, the issue of sanctions has been deferred.

22) The FDA, which regulates prescription drugs, apparently prohibits its employees from entering into such agreements. Are policies that govern these two HHS agencies different? If so, why?

FDA is a unique consumer protection and regulatory agency within the Department and has had regulatory restrictions on certain outside activities since 1972. FDA employees participate in regulatory and product approval matters that substantially affect significant sectors of the United States economy, including the food, pharmaceutical, medical device, and biotechnology industries. In addition, many FDA employees have access to confidential information and trade secrets. Further, Many FDA employees participate in enforcement matters, including seizures, injunctions, and criminal prosecutions. Therefore, FDA has compelling reasons to impose certain restrictions on outside employment activities between its employees and entities regulated by FDA. See 61 Fed. Reg. 39757-8 (July 30, 1996).

APPENDIX

DHHS ACTIONS RELATED TO
THE 1998 RECOMMENDATIONS OF ITS INSPECTOR GENERAL
REGARDING PROTECTION OF HUMAN RESEARCH SUBJECTS

OPRR/NIH and FDA Actions on 1998 OIG recommendations

(1a) Eliminate or lessen procedural requirements.

(i) OPRR (in cooperation with FDA) expanded the research categories that may be reviewed using expedited procedures. (ii) OPRR harmonized its guidance with that of FDA to permit IRB meetings to be convened via telephone conference calls. (iii) OPRR issued guidance permitting IRBs to utilize Data and Safety Monitoring Board (DSMB) reports in the continuing review process. (iv) OPRR expects to implement plans for a simplified and streamlined Assurance process by the end of this calendar year.

FDA is actively reviewing and revising its FDA Information Sheets for IRBs and Clinical Investigators to more clearly define its requirements and to remove those that are not supported by existing regulations. This will require approximately a year to complete.

(1b) Require performance focused evaluations of IRBs.

Performance standards for IRBs have been quite difficult to develop. OPRR is working with Public Responsibility in Medicine & Research (PRIM&R) to develop accreditation procedures that will utilize performance based standards for IRBs. It is premature to require such performance focused evaluations before meaningful performance standards are developed.

FDA currently is looking at performance measures that can be incorporated into its inspectional process to fulfill this recommendation.

(2a) Require DSMBs for some multi-site trials.

OPRR has issued guidance permitting IRBs to utilize Data and Safety Monitoring Boards (DSMB) in the continuing review process. Requiring DSMBs for certain types of trials could entail modification of the Federal Policy (Common Rule) for the Protection of Human Subjects. If so, such a modification would require identical and coordinated rulemaking by 17 separate departments and agencies.

FDA has created a working group to examine the role and responsibilities of DSMBs and when they should be required. This working group is actively working on a guidance document.

(2b) Provide IRBs with feedback on developments concerning multisite trials.

In order to encourage such feedback, OPRR issued guidance permitting IRBs to utilize Data and Safety Monitoring Board (DSMB) reports in the continuing review process. Requiring such feedback could entail modification of the Federal Policy (Common Rule) for the Protection of Human Subjects. If so, such a modification would require identical and coordinated rulemaking by 17 separate departments and agencies.

In addition to the DSMB working group (see above), which will look at the issue of whether information from DSMBs should be shared with IRBs, FDA has a working group on adverse event reporting. This working group is looking at the information currently provided to IRBs to determine how it can be made more meaningful and less burdensome and ultimately provide better protection to the subjects involved in research.

(2c) Provide IRBs with feedback about FDA actions against investigators.

FDA has modified its Privacy Act Systems Notice in order to permit FDA to share findings from clinical investigator inspections with IRBs and sponsors involved in the clinical investigator's study(ies).

(2d) Require sponsors and investigators to notify IRBs of prior reviews.

Requirements for sponsors are not applicable to OPRR. Requiring such notification by investigators could entail modification of the Federal Policy (Common Rule) for the Protection of Human Subjects. If so, such a modification would require identical and coordinated rulemaking by 17 separate departments and agencies. Although FDA could effect this recommendation unilaterally by appropriate modifications to its regulations, such action would be most effective if it were taken in concert with corresponding changes in the Common Rule.

(2e) Call for increased IRB awareness of on-site research practices.

OPRR is considering developing guidance calling for increased IRB awareness of on-site research practices.

(3a) Require institutions to educate investigators on human subject protections.

OPRR's new Assurance process will require that institutions provide a program of such training for investigators.

(3b) Require investigator attestation to human subject protections.

Requiring investigator attestations could entail modification of the Federal Policy (Common Rule) for the Protection of Human Subjects. If so, such a modification would require identical

and coordinated rulemaking by 17 separate departments and agencies.

(3c) Require education programs for IRB members.

OPRR's new Assurance process will require that institutions provide a program of such training for IRB members.

(4a) Require more representation on IRBs of nonscientific and noninstitutional members.

OPRR is considering developing guidance calling for more representation on IRBs of nonscientific and noninstitutional members. Requiring more representation could entail modification of the Federal Policy (Common Rule) for the Protection of Human Subjects. If so, such a modification would require identical and coordinated rulemaking by 17 separate departments and agencies.

(4b) Reinforce to institutions the importance of IRBs having sufficient independence.

OPRR has required corrective action at selected institutions where such independence was suspect. OPRR is considering developing guidance to reinforce the importance of IRB independence.

(4c) Prohibit IRB equity owners from participating in the IRB review process.

OPRR has prohibited such participation for a number of years. For FDA to do so would require amendment to the FDA regulations.

(5a) Require adequate resources for IRBs.

The Federal Policy (Common Rule) requires adequate staffing of IRBs; the FDA regulations do not contain a similar explicit requirement. Moreover, OPRR has required corrective action where it has found such staffing to be inadequate. OPRR is working with Public Responsibility in Medicine & Research (PRIM&R) to develop accreditation procedures that will utilize performance based standards for IRBs that will require adequate resources.

(6a) Revamp the OPRR Assurance Process.

OPRR expects to implement plans for a simplified and streamlined Assurance process by the end of this calendar year.

(6b) Revamp the FDA Inspection Process.

FDA is reassessing its inspections process to determine what refinements might realistically be undertaken within available resources.

(6c) Require registration of IRBs.

All institutions receiving DHHS support for human subject research are already required to register the IRBs responsible for that research in the form of an Assurance to OPRR. FDA has identified the information that would be collected during registration as well as the method of collection. However, implementation will require change in the FDA regulations and sufficient resources. Neither FDA nor OPRR currently has authority to require registration of all IRBs in the United States. We are currently reviewing what legislation would be required to do this.

NIH implementation of OIG 1998 recommendations

(1) Require investigator attestation to human subject protections

- Beginning in October 2000, the NIH will require investigators engaged in clinical research to obtain education in the fundamentals of protection of human subjects. NIH will review the credentials of these investigators before funding is made for their projects.

- The NIH currently requires the intramural clinical investigators and extramural managers who have oversight responsibility for clinical projects to be educated in the special requirements for protection of human subjects. The training is also available for download and use by staff in other organizations beyond the NIH. The training can be found at: **http://helix.nih.gov:8001/ohsr/newcbt/**.

- The NIH has mounted a series educational efforts targeting different audiences, such as investigators and individuals who comprise IRBs. We offer some examples below:

- In 1999, the NIH launched a web site on bioethics. It can be accessed at http://www.nih.gov/sigs/bioethics/. *Bioethics Resources on the Web* is designed to facilitate research, scholarly activities, and training. The web site also links to related sites, such as university ethics programs, medical and biotech sites, the Federal Register, and ethics journals. We believe that this web site serves as a valuable information resource for IRB members, providing education and information about ethical, legal, and regulatory issues on human subjects participating in research.

- In 1999, the NIH re-issued two program announcements related to education in bioethics. One provided support for short-term courses in research ethics, the other a mentored scientist development award in research ethics. The primary objective of the short-term courses is to increase investigators' knowledge of research ethics to protect research subjects. To date, NIH has made 15 awards. In addition, NIH offers career development awards that are specifically designed for individuals who are committed to a career in research ethics. It is envisioned that individuals completing this program of study will serve as leaders in the field, educating the broader population of investigators about crucial issues in the ethical conduct of research. In addition, every predoctoral and postdoctoral trainee receiving an NIH National Research Service Award (NRSA) is

required to receive training in the responsible conduct of research. The application for these awards must include a description of a program that will provide instruction in scientific integrity and other aspects of ethical research.

Moderate workload pressures of IRBs

- The NIH has undertaken a major initiative to reduce regulatory burdens on grantee institutions to improve effectiveness and efficiency of the overall mission. This initiative focuses on five areas, one of which is human subjects protection. A recent report issued by the Regulatory Burden Advisory Group offered several recommendations to improve procedural requirements of IRBs. This report is available on the NIH website at http://grants.nih.gov/grants/policy/regulatoryburden.

- The NIH has recently implemented "just-in-time" IRB review of research protocols. Under this plan, investigators may submit grant applications to IRBs for review after they have received a peer review score that is likely to result in funding. This change in grants policy should reduce the work load of IRBs by eliminating those projects that are not likely to be funded by the NIH. Similarly, this change should focus IRB resources on the review of studies that are very likely to be implemented.

Require DSMBs to provide summary information to IRBs

- In 1999, the NIH issued guidance on the reporting of adverse events for clinical trials. Because it can be difficult for IRBs to assess individual adverse events, this guidance requires Data Safety Monitoring Boards (DSMB) to provide IRBs with summary reports of their discussions of aggregated data on adverse events.

Strengthen continuing protections for human subjects participating in research

- The NIH has a long standing policy, since 1979, requiring data and safety monitoring for all clinical trials. In 1998, the NIH re-issued a similar policy reaffirming the requirement for some form of data and safety monitoring for all clinical trials, not just Phase III or multi-site trials. The NIH views DSMBs and IRBs as having complementary roles in the assessment of risks and ultimately the protection of research participants. Thus, as noted above, NIH policy encourages DSMBs to provide summary information on adverse events to IRBs.

- Beginning in October 2000, the NIH will require investigators doing phase I or II clinical trials to submit their data and safety monitoring plans to the NIH for review and approval.

- As part of a new pro-active grants compliance program, the NIH is organizing ten site visits to NIH-funded institutions. Three of these were completed in March, 2000. These visits will involve a review of institutional understanding of, and compliance with, a range of NIH rules, regulations, and guidelines.

Insulate IRBs from conflicts that can compromise their mission in protecting human subjects

- The NIH is collaborating with DHHS in developing a public conference this summer to discuss conflicts of interest pertaining to institutions, individual investigators, and IRB members.

Provide sufficient resources to IRBs

- IRBs are under increased pressure in their job, sometimes with insufficient resources. While it is the responsibility of the institutions to ensure that their IRBs have the resources to fulfill their duties, NIH and FDA are discussing with the institutions strategies to assess the current adequacy of those resources and ways to improve them, if needed.

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